CLINICAL STUDY PROTOCOL 4.0
AMENDMENT 3.0

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PARALLEL-GROUP PHASE II STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF TWO DIFFERENT DOSE REGIMENS OF IFX-1 AS ADD-ON TO STANDARD OF CARE IN SUBJECTS WITH GRANULOMATOSIS WITH POLYANGIITIS (GPA) AND MICROSCOPIC POLYANGIITIS (MPA)

Study Number: IFX-1-P2.6

Study Product: IFX-1

IND Number: 137457

Sponsor: InflaRx GmbH
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Version and Date of Protocol: Version 4.0
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Amendment: Version 3.0

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LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANCA	anti-neutrophil cytoplasmic antibody
anti-HBc	hepatitis B core antigen
AZA	azathioprine
BVAS	Birmingham Vasculitis Activity Score
CH50	50% hemolytic complement
CHCC	Chapel Hill Consensus Conference
CMO	Contract Manufacturing Organization
CRO	Contract Research Organization
CRP	C-reactive protein
CYC	cyclophosphamide
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay test
FAS	Full analysis set
FSH	follicle-stimulating hormone
GBM	glomerular basement membrane
GC	glucocorticoid
GCP	Good Clinical Practice
GPA	granulomatosis with polyangiitis
GTI	Glucocorticoid Toxicity Index
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IDMC	Independent Data Monitoring Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IWRS	Interactive Web Response System
MAC	membrane attack complex
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MPS	mycophenolate sodium
MTX	methotrexate
NaCl	sodium chloride
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
PR3	proteinase 3
PRO	patient-reported outcome
RTX	rituximab
SAE	serious adverse event
SAF	Safety analysis set
SF-36	36-item Short Form survey
SOC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UACR	urinary albumin:creatinine ratio
ULN	upper limit of normal
VDI	Vasculitis Damage Index

DEFINITION OF TERMS

Baseline	A value or quantity that serves as a reference for comparisons over time.
Central laboratory	A laboratory where all subject-derived samples (e.g., serum, plasma) are centrally analyzed and if necessary, distributed for analysis to specialized laboratories.
Compliance	Adherence to all the study-related requirements, Good Clinical Practice requirements, and the applicable regulatory requirements.
Clinical remission	BVAS = 0
Clinical response	Reduction in BVAS of ≥50% from Baseline and no worsening in any body system.
Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed eligible or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
Electronic case report form	An electronic form for recording subjects' data during the study, as required by the protocol.
End of Study	Overall study completion: the day of the last visit of the last subject in the study. Individual subject: the time point after which no further study-related procedures are performed.
Endpoint	Key measurement or observation used to measure the effect of experimental variables in a study.
Enrollment	The time point at which a subject formally starts to participate in the study by signing an informed consent form.
Follow-up Period	After IMP administration in Week 16 to Week 24, during which no IFX-1 or placebo is given.

Investigational medicinal product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in the current study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form.
Limited disease flare (minor relapse)	Any new occurrence or worsening of one or more of the minor BVAS items listed in Appendix 18.4 after clinical remission (BVAS = 0).
Remission Induction Phase	The time from the start of remission induction therapy until clinical remission (BVAS = 0), during which RTX or CYC plus GCs are given as standard of care.
Remission Maintenance Phase	The time from clinical remission until Week 24, during which subjects are allowed to change standard of care.
Safety follow-up visit	To be performed for any subject who discontinues from the study during the Treatment Period (i.e., until Week 16) at 1 month (±3 days) after the last IMP administration.
Screening	The predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for randomization into the study.
Severe disease flare (major relapse)	BVAS >3 or experiencing one of the major BVAS items listed in Appendix 18.4 that requires treatment with other than permitted AAV therapy after clinical remission (BVAS = 0).
Standard of care	RTX or CYC administration plus standard dose glucocorticoids (GCs) in the Remission Induction Phase. RTX, CYC, AZA, MTX, MMF, or MPS plus standard dose GCs (if tapering is still ongoing) in the Remission Maintenance Phase.

Study start	The time point at which the first subject gives written informed consent; equivalent to first subject's first visit at the first study site which has enrolled a subject into the study.
Treatment Period	Week 0 to Week 16, during which IFX-1 or placebo is given as add-on to standard of care.

STUDY SYNOPSIS

Title of Study:

A randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase II study to investigate the safety and efficacy of two different dose regimens of IFX-1 as add-on to standard of care in subjects with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Protocol / Study Number: IFX-1-P2.6

Type of Study:	**Indication:**
Safety study	GPA and MPA indicated for therapy with cyclophosphamide (CYC) or rituximab (RTX) and standard dose glucocorticoid (GC) therapy

Sponsor: InflaRx GmbH

Coordinating Investigator: [redacted], **MD, MPH**

Study Site(s):

Approximately 38 sites in the United States of America and Canada

Phase of Development: II

Objectives:

Primary Objective:

The primary objective is to investigate the safety and tolerability of two dose regimens of IFX-1 as add-on to standard of care (SOC) in subjects with GPA and MPA compared with placebo

Secondary Objectives:

- To investigate the clinical response of two dose regimens of IFX-1 in subjects with GPA and MPA compared with placebo.
- To generate data for pharmacokinetic (PK) and pharmacodynamic (PD) modeling for two dose regimens of IFX-1.

Methodology:

This is a prospective, randomized, double-blind, placebo-controlled, parallel-group (three treatment groups), multicenter, Phase II study. For each subject, the study will comprise a Screening Period (up to 2 weeks), a Treatment Period (Week 0 to Week 16), and a Follow-up Period (after investigational medicinal product [IMP] administration in Week 16 to Week 24).

All subjects will receive the IMP, i.e., IFX-1 (400 mg or 800 mg) or placebo from Week 0 to Week 16 (i.e., during the Treatment Period). All subjects will receive SOC during the Treatment and Follow-up Periods. From Week 0 up to clinical remission (Remission Induction Phase). Only the following SOC will be allowed during this phase:

- RTX or CYC
- Standard dose of GCs

Following clinical remission and up to Week 24, subjects are allowed to switch to other SOC (azathioprine [AZA]/methotrexate [MTX]/mycophenolate mofetil [MMF]/mycophenolate sodium [MPS] plus GCs), to use throughout the remainder of the study, or to stay on RTX or CYC (Remission Maintenance Phase).

A PK substudy will be conducted in 15 subjects who provide additional consent for participation in this substudy. Blood samples for the PK substudy will be collected at Weeks 1, 4, and 16.

Number of Subjects:

A total of 36 subjects are planned to be randomized in the study in a 1:1:1 ratio to three treatment groups (Groups A, B, and C). Approximately 24 subjects in the active treatment groups and 12 subjects in the placebo group are considered to be sufficient, based on medical evaluation, to investigate the safety and tolerability of IFX-1 as add-on to SOC in subjects with GPA and MPA.

Study Population:

Subjects must meet all of the following inclusion criteria at Screening to be randomized into the study:

1. Male or female, ≥18 years of age.
2. Written informed consent obtained from subject.
3. Diagnosis of GPA or MPA according to the definitions of the Chapel Hill Consensus Conference.
4. Have at least one "major" item, or at least three other (minor) items, or at least two renal items on the Birmingham Vasculitis Activity Score (BVAS) Version 3.0.
5. New or relapsed GPA or MPA that require treatment with CYC or RTX plus GCs.
6. Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m^2.
7. History of positive antigen-specific anti-neutrophil cytoplasmic antibody (ANCA) test through a documented positive ELISA test for either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) antibodies. For newly diagnosed subjects a recent positive ELISA testing for either anti-PR3 or anti-MPO is mandatory for inclusion.

Subjects who fulfill any of the following exclusion criteria at Screening are not eligible to participate in the study:

1. Any other multisystem autoimmune disease as listed in Appendix 18.5.
2. Requires mechanical ventilation because of alveolar hemorrhage at screening.
3. Have required management of infections, as follows:

    a. Chronic infection requiring suppressive anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster or atypical mycobacteria)

    b. Use of intravenous antibacterials, antivirals, anti-fungals, or anti-parasitic agents.
4. Known or suspected active drug and/or alcohol abuse.
5. Human immunodeficiency virus, hepatitis B, or hepatitis C viral screening test showing evidence of active or chronic viral infection at Screening or a documented history of the human immunodeficiency virus, hepatitis B, or hepatitis C.
6. One of the following abnormal laboratory findings at Screening:
    - White blood cells $<3500/mm^3$
    - Platelet count $<120,000/mm^3$
    - Total bilirubin >3 times the upper limit of normal (ULN)
    - Alanine aminotransferase or aspartate aminotransferase >5 x ULN
7. Acute or chronic liver disease.
8. Known hypersensitivity to inactive ingredients of the GC capsules.
9. History of or active malignancy, lymphoproliferative or myeloproliferative disorder. Individuals with squamous cell or basal cell carcinomas of the skin and individuals with cervical carcinoma in situ who have received curative surgical treatment may be eligible for this study.
10. History of anti-glomerular basement membrane disease.
11. Received CYC or RTX within 12 weeks before Screening; if on azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or mycophenolate sodium (MPS) at the time of Screening, these drugs must be withdrawn prior to receiving CYC or RTX.
12. Received more than 3 g cumulative intravenous GCs within 4 weeks before Screening.
13. Received an oral daily dose of a GC of more than 10 mg prednisone equivalent for more than 6 weeks continuously prior to Screening.
14. Received a CD20 inhibitor, anti-tumor necrosis factor treatment, abatacept, alemtuzumab, any other experimental or biological therapy, intravenous

immunoglobulin or plasma exchange, antithymocyte globulin, or required dialysis within 12 weeks before Screening.

15. Received a live vaccination within 4 weeks before Screening or planned between Screening and Week 24.
16. Subjects with a history of tuberculosis.
17. Pregnant or lactating.
18. Clinically significant abnormal electrocardiogram during Screening, e.g., QTcF >450 ms.
19. Female subjects of childbearing potential unwilling or unable to use a highly effective method of contraception (pearl index <1%) such as complete sexual abstinence, combined oral contraceptive, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant, or depot contraceptive injection in combination with a second method of contraception such as condom, cervical cap, or diaphragm with spermicide during the study and for at least 4 weeks after last administration of IFX-1 (timeframes for SOC have to be considered as described in the respective Prescribing Information).
    Male subjects with female partners of childbearing potential unwilling to use contraception (condoms) during treatment and for at least 4 months after last administration of treatment.
20. Evidence or suspicion that the subject might not comply with the requirements of the study protocol.
21. Any other factor which, in the investigator's opinion, is likely to compromise the subject's ability to participate in the study.
22. The subject is an employee or direct relative of an employee at the study site or sponsor.
23. The subject is imprisoned or lawfully kept in an institution.
24. The subject has participated in an investigational clinical study during the 12 weeks (or five times the half-life of the previous IMP, whichever is longer) before Screening, or plans to participate in another investigational clinical study during their participation in this study.

Test Product, Dose, and Mode of Administration:

Subjects in Group A will receive 400 mg IFX-1 (low dose) and subjects in Group B will receive 800 mg IFX-1 (high dose). IFX-1 will be provided in 10 mL vials containing 100 mg IFX-1 and will be infused after dilution in sodium chloride (NaCl) over a period of approximately 30 to 60 minutes via an intravenous line.

Reference Therapy, Dose, and Mode of Administration:

Subjects in Group C will receive placebo. The placebo will be provided in 10 mL vials containing NaCl, sodium phosphate, and Polysorbate 80. The placebo vials and content will have the same appearance as the IFX-1 vials and additives and will be administered in the same manner as IFX-1.

Study Duration:

The study duration for an individual subject will be up to 26 weeks: a 2-week Screening Period, a 16-week Treatment Period, and an 8-week Follow-up Period.

Criteria for Evaluation

Primary Endpoint:

- Number and percentage of subjects who experience at least one treatment-emergent adverse event (TEAE) per treatment group

Secondary Endpoints:

- IMP-related serious adverse events (SAEs)
- IMP-related TEAEs
- Adverse events of special interest
- Proportion of subjects achieving clinical response (defined as a reduction in BVAS of ≥50% and no worsening in any body system) at Week 16
- Proportion of subjects with clinical remission (BVAS = 0) at Week 16
- IFX-1 concentration pre- and postdose at each IMP administration visit (during the Treatment Period at Weeks 0 to 16) until Week 20
- IFX-1 concentration [redacted] in the PK substudy
- Absolute and relative change from baseline, if applicable, in C5a, 50% hemolytic complement (CH50), C-reactive protein (CRP), and IFX-1 blocking activity at each measured time point

Statistical Methods:

The safety of the subjects will be monitored by an unblinded Independent Data Monitoring Committee.

In general, data will be analyzed by treatment group and will be differentiated further (e.g., by visit). [redacted].

For the analysis of the primary safety endpoint, the number and percentage of subjects who experienced at least one TEAE will be presented. Additionally, the number of TEAEs will be analyzed by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. All subsets of TEAEs (e.g., related TEAEs) will be analyzed in the same way as the primary endpoint.

Continuous safety and efficacy parameters will be analyzed by descriptive statistics for absolute values and changes from baseline (absolute and relative) by time point and treatment group, as applicable. Categorical safety and efficacy parameters will be summarized by absolute and relative frequencies by time point and treatment group.

The number and percentage of subjects presenting ADA and ANCA antibodies will be displayed by time point and treatment group. Actual sampling times and IFX-1 plasma concentrations will be tabulated. Results from the PK substudy will be analyzed using a PK model and will be reported separately. For the analysis of PD, plasma concentrations of C5a, and IFX-1 blocking activity will be analyzed by each time point specified in the Schedule of Assessments and also as change from Baseline, if applicable. All biomarkers will be analyzed descriptively by time point and treatment group.

SPONSOR SIGNATURE PAGE

Protocol / Study Number: IFX-1-P2.6

Confirmation of the Final Protocol Amendment 3.0, dated 25 March 2019

I hereby certify that this is the final version of the protocol amendment:

Study Title: A randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase II study to investigate the safety and efficacy of two different dose regimens of IFX-1 as add-on to standard of care in subjects with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Sponsor's Responsible Medical Officer:

Date

[redacted], MD

[redacted]

Tel: [redacted]

COORDINATING INVESTIGATOR SIGNATURE PAGE

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Herewith I declare that I have read and understood the present protocol and agree to honor each part of it. By signing this study protocol, I agree to conduct the clinical study, following approval by an Ethics Committee, in accordance with the study protocol, the current International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all the subjects enrolled in the study by my site will be treated, observed, and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product, and their duties.

Coordinating Investigator:

Date

[redacted], MD, MPH

[redacted]

INVESTIGATOR SIGNATURE PAGE(S)

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_____

A separate signature page should be created for each principal investigator.

Names and affiliations to be filled out by the investigator.

Principal Investigator:

Name and affiliation _____

_____

_____ _____

Date <Insert name>

1 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is applicable to all subjects.

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU	USV[n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
Informed consent	X																
Inclusion/exclusion criteria	X																
Pregnancy test [c]	X		X						X				X		X	X	
Demographics and baseline characteristics [d]	X																
Body weight	X		X				X		X		X		X	X	X	X	X
Medical history	X																
36-item Short Form survey [e]			X										X		X	X	
BVAS	X		X				X		X		X		X	X	X	X	X
VDI			X										X		X	X	X
PGA			X		X	X	X		X		X		X	X	X	X	X

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU	USV[n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
GTI			X [f]										X		X	X	X
Vital signs [g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X												X		X	X	
Physical examination	X												X		X	X	
IMP administration: IFX-1 or placebo			X	X	X	X	X	X	X	X	X	X	X				
Standard of care [h]	◄												►				X
Safety laboratory measurements [*]	X		X				X		X		X		X	X	X	X	X
Serology: HIV/hepatitis B/hepatitis C virus	X																
ANCA testing	X					X	X		X		X		X		X	X	
Anti-GBM	X																
Serum sample total protein	X		X		X	X	X		X		X		X	X	X	X	X
Urinalysis [i]	X		X		X	X	X		X		X		X	X	X	X	X
PK: IFX-1 level [redacted]			X	X	X [k]	X	X [k]	X	X	X	X	X	X [k]	X	X	X	

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU	USV[n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
PD: C5a [redacted]			X	X	X	X	X		X		X		X	X	X	X	
Biomarker: CH50 (serum)			X		X	X	X		X		X		X	X	X	X	
Biomarker: CRP (serum)			X		X	X	X		X		X		X	X	X	X	
PD: IFX-1 blocking activity [redacted]						X							***X***	***X***	***X***	X	
Anti-drug antibodies (serum)			X			X	X		X		X		X	X	X	X	
[redacted]			X	X	X	X	X		X		X		X	X	X	X	
[redacted]			X				X		X		X		X	X	X	X	
[redacted]			X				X		X		X		X	X	X	X	
Adverse events	X		←										→			X	X
Concomitant therapy	X [m]		←										→			X	X

ANCA = anti-neutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; CH50 = 50% hemolytic complement; CRP = C-reactive protein; [redacted] EOS = End of Study; GBM = glomerular basement membrane; GTI = glucocorticoid toxicity index; HIV = human immunodeficiency virus; IMP = investigational medicinal product; MCP = monocyte chemoattractant protein; PD = pharmacodynamics; PGA = Physician Global Assessment; SFU = Safety Follow-Up Visit; SOC = standard of care; VDI = Vasculitis Damage Index

a Randomization can be performed at any time between completion of the screening assessments and the first IMP administration on Day 1.

b These assessments should be performed at:
- Week 24 for subjects who complete the study.
- The time when a subject's participation in the study is discontinued if the subject is prematurely discontinued from the study.
- Safety follow-up visit: 1 month (±3 days) after the last IMP administration for any subject who discontinues from the study until Week 16 (i.e., during the Treatment Period).

c Only in women of childbearing potential. To be performed in serum at Screening and Week 24 and in urine (using a dipstick) at the other indicated visits. For any subjects who discontinue participation until Week 16, a serum pregnancy test should be performed both at the time of discontinuation and at the safety follow-up visit.

d Demographics and baseline characteristics include age, gender, race and ethnicity, height, and smoking status.

e The questionnaire should be completed at the study site before any other assessments are performed.

f Only baseline laboratory parameters and symptoms of the specific list of GTI will be assessed.

g Vital signs include: systolic and diastolic blood pressure, pulse rate (counted for at least 30 seconds after 5 minutes in a sitting position), respiratory rate, and body temperature.

h All subjects will use SOC during the Treatment and Follow-up Periods. From Week 0 up to clinical remission (Remission Induction Phase), only rituximab or cyclophosphamide plus GCs will be allowed. Following clinical remission and up to Week 24, subjects are allowed to switch to other SOC (azathioprine/methotrexate/ mycophenolate mofetil/mycophenolate sodium plus GCs), to use throughout the remainder of the study, or to stay on RTX or CYC (Remission Maintenance Phase).

i Urinalysis includes creatinine, total protein, albumin, and MCP-1; all to be analyzed at a central laboratory. [redacted] All derived ratios and the estimated glomerular filtration rate will be calculated at the time points when the respective single serum or urinary parameters are planned to be assessed.

[redacted]

m Prior therapy will be recorded at Screening.

n In case of major or minor relapse.

* Additional safety laboratory parameters according to the respective United States Prescribing Information are recommended as follows:
Cyclophosphamide: blood sampling, including complete blood count and serum creatinine, to be obtained before each CYC IV administration and for oral administration at least every 2 weeks.
Methotrexate: complete blood count with differential and platelet counts, hepatic enzymes, renal function tests to be obtained before starting treatment with methotrexate.
AZA, MMF, MPS: For patients that are newly treated: complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION ON THE INDICATION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are related systemic vasculitides that, along with eosinophilic granulomatosis with polyangiitis (Churg-Strauss), are grouped under the term anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Both GPA and MPA are associated with ANCA, have many identical clinical manifestations, have many similar histologic features, and have similar outcomes. GPA and MPA predominantly affects small vessels and are associated with myeloperoxidase-ANCA (MPO-ANCA) or proteinase 3 (PR3-ANCA). Although neither sensitive nor specific, common complaints and signs of GPA and MPA include fatigue, fever, weight loss, arthralgia, rhinosinusitis, cough, and dyspnea, urinary abnormalities (an active urine sediment) with or without renal insufficiency, purpura, and neurologic dysfunction. These forms of vasculitis can present and progress slowly over months or explosively over days. If untreated, GPA and MPA progresses from a limited disease process (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase, characterized by multiple complications of small-vessel vasculitis (i.e., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) [Rheinhold-Keller 2004].

GPA and MPA most commonly occur in older adults, although these diseases have been reported at all ages [Jennette 1997, Seo 2004]. Men and women are equally affected, and the diseases are far more common among white individuals than those of other races/ethnicity [Falk 1990].

The incidence of these conditions in the United States of America is approximately 6,000 new cases per year, and the estimated prevalence is 25,000 to 30,000 ***cases*** [Watts 2015]. The overall incidence rates of AAV in Europe are reported to be in the range of 13 to approximately 20 ***per*** million [Watts 2015]. The prevalence of AAV is estimated to be 46 to 184 ***per*** million [Ormerod 2008, Reinhold-Keller 2000]. The prevalence of AAV has generally increased over the last 20 years, and this could reflect improved patient survival and case identification, e.g., by using multiple retrieval sources [Watts 2015].

The Standard of Care as recommended in the guideline for AAV [Yates 2016] usually consists of rituximab (RTX) or cyclophosphamide (CYC) administration for remission-induction, with glucocorticoid (GC) tapering followed by azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or mycophenolate sodium (MPS) for remission-maintenance. Alternatively, a second cycle of RTX can be given.

Although treatment failures and disease relapses decreased due to the improvement of remission-induction regimens during recent years, patients with MPA and GPA treated with conventional regimens have a 9-fold increased mortality risk in the first year

attributed to infection, cardiovascular disease, malignancies, vasculitis activity, and renal disease [Luqmani 2011 a, Flossmann 2011]. It is proven that current therapies contribute to more than half of this increased risk rather than the underlying disease itself [Little 2010]. Most of the side effects are attributed to the high-dose of GCs, which are still part of Standard of Care for MPA and GPA. GCs have long-term side effects such as osteoporosis, Cushing's syndrome, increased infection risk and risk of diabetes mellitus [Goupil 2013, Moghadam-Kia 2010, Charlier 2009, McGregor 2012], and progressive organ damage [Robson 2015]. Therefore, the replacement of GCs by IFX-1 may improve the short- and long-term safety of treatment of MPA and GPA for the induction of remission.

2.2 BACKGROUND INFORMATION ON IFX-1

IFX-1 is a monoclonal antibody which specifically binds to the soluble human complement split product C5a. Nonclinical studies have demonstrated that IFX-1 binds to its target rapidly and is capable of a nearly complete blockade of C5a-induced biological effects while not affecting cleavage of C5 and formation of the complement membrane attack complex (MAC).

[redacted]

Various nonclinical studies have been conducted to assess pharmacological and toxicological aspects of IFX-1, none of which revealed any obvious toxicological or safety concerns for IFX-1. IFX-1 was well tolerated and did not show any toxicity with any of the doses tested.

IFX-1 is an investigational medicinal product (IMP) and is not approved in any country worldwide. To date, IFX-1 has been investigated in one Phase I study in healthy subjects and in three Phase II studies: in subjects with early septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with moderate to severe hidradenitis suppurativa (HS).

[redacted] Based on the study data available, IFX-1 was safe and well tolerated when administered to healthy subjects and patients.

In addition to GPA and MPA, IFX-1 is also in clinical development for moderate to severe HS.

[redacted]

2.3 RATIONALE FOR THE STUDY

AAV is a group of potentially life-threatening autoimmune diseases. Experimental data from animal models and in vitro experiments demonstrate that primed neutrophils are activated by ANCA and generate C5a that engages C5a receptors on neutrophils. As expected, patients with ANCA-related disease have elevated plasma and urine levels of C5a in active disease and not in remission [Chen 2017].

Given the mode of action of IFX-1 as a monoclonal antibody specifically binding to the soluble human complement split product C5a and the resulting nearly complete blockade of C5a-induced biological effects, it may be effective in the treatment of subjects with AAV.

IFX-1 was safe and well tolerated in other life-threatening indications like sepsis and cardiac surgery, and long-term data are available from a clinical study in HS. However, safety data of IFX-1 in combination with standard of care (SOC) for GPA and MPA are not yet available.

The aim of this study is to evaluate the safety of two dose regimens of IFX-1 as add-on SOC for GPA and MPA. Furthermore, the study will collect data on efficacy and patient-reported outcomes (PROs) of two different dose regimens of IFX-1 in comparison with placebo that could be positively affected by a C5a blocking therapy.

2.3.1 Study Population

Patients with newly diagnosed or relapsed GPA or MPA that require treatment with rituximab (RTX) or cyclophosphamide (CYC) plus standard dose glucocorticoids (GCs) will be randomized in this study. Patients with life-threatening symptoms will not be randomized because IFX-1 has not yet been investigated in this indication.

The exclusion criteria (Section 4.2) will ensure that the study population is as homogenous as possible.

2.3.2 Dosing Regimen

The aim of treatment with IFX-1 is to achieve almost complete blockade of the overall available C5a (existing and newly produced) in human whole blood during the entire treatment period.

[redacted] According to available data and derived estimates, dosing with

800 mg every 2 weeks will result in mean IFX-1 trough levels in the range of 10 to 20 µg/mL, which, based on available data, should result in a complete blocking of C5a over the entire treatment period.

Based on the assumption that the trough level for 800 mg dosing is 4 to 20 µg/mL, the trough level for 400 mg should be in the range of 1 to 5 µg/mL two weeks after dosing. According to the available data, this level of drug should be able to keep C5a level under the normal control levels by the end of the treatment period.

The toxicological profile of IFX-1 is considered adequate to support dose levels of 800 mg IFX-1 for a time period of 16 weeks. There were no relevant findings in the toxicology studies, which would preclude the continued clinical development of IFX-1.

2.3.3 Study Design

This will be the first study conducted in patients with GPA and MPA and the double-blind, placebo-controlled design is deemed appropriate for the primary objective of this study (i.e., to monitor the safety of patients with GPA and MPA when IFX-1 is administered at two different doses in combination with SOC).

A control group will be used to evaluate the safety and efficacy of the two IFX-1 doses compared with placebo. The use of placebo as the control is justified as subjects will continue to receive SOC throughout the study in the active groups and the placebo group. Both the subjects and the study site personnel (including the investigator) will be blinded to minimize any bias. The half-life of IFX-1 is expected to be 3 to 4 days in GPA and MPA patients and in order to achieve steady-state faster, all subjects will receive four administrations of the IMP during the first 2 weeks (on Days 1, 4, 8, and 15). Thereafter, subjects will receive the IMP once every 2 weeks, the planned regimen of IFX-1 to be used for the treatment of GPA and MPA.

The study will be conducted in compliance with this study protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), and the applicable regulatory requirements.

2.3.4 Expected Benefits

The subjects who will be treated with IFX-1 or placebo in this study will benefit from an improvement in GPA and MPA-related symptoms since all subjects will receive SOC for GPA and MPA and therefore all subjects will receive the best possible treatment for their disease. As two-thirds of the subjects will additionally receive IFX-1, they may experience a faster response to treatment.

2.4 RISK-BENEFIT ASSESSMENT

Considerations on risk-benefit-related aspects are derived from nonclinical data and clinical Phase I data in healthy subjects, as well as from clinical data from three other Phase II studies conducted in subjects with early, newly developing abdominal or pulmonary derived septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with HS. In addition, the mode of action of IFX-1 is clearly supported in subjects with GPA and MPA [Van Timmerman 2012].

2.4.1 Potential Risks

No subject with GPA or MPA has been treated with IFX-1 to date, but IFX-1 was generally well tolerated in other studies and no new risks are anticipated. Subsequently, no subject with GPA or MPA has been treated with IFX-1 in combination with SOC, therefore the drug-drug interactions, safety, tolerability, and efficacy of IFX-1 have not yet been investigated.

Potential and theoretical risks associated with administration of IFX-1 may include infections, meningitis/meningococcal septicemia, and anaphylactic reactions/acute allergic hypersensitivity (Section 6.4.1).

The major side effects associated with the use of GCs are listed in Appendix 18.2.

2.4.2 Risk Associated with Lack of Efficacy

RTX or CYC and standardized GC tapering will be administered as the SOC until clinical remission (i.e., during the Remission Induction Phase) and can be given after clinical remission at the discretion of the investigator. Due to the treatment response rate of up to 90% of this established remission induction therapy, the risk of lack of efficacy is deemed to be very low in this study. In accordance with the current guidelines for AAV, subjects can further receive AZA, MTX, MMF, or MPS after clinical remission as deemed appropriately by the investigator [Yates 2016]. In case of any relapses, immediate treatment, as described in Section 7.3, is foreseen to avoid harm to the subjects.

With the administration of IFX-1 or placebo, no deterioration in health status is expected with respect to GPA and MPA [redacted].

In addition, an unblinded Independent Data Monitoring Committee (IDMC) will monitor the safety of the subjects and the study can be terminated by the IDMC. The same applies to the Investigator or the subject, who can prematurely discontinue the study.

2.4.3 Conclusion

GPA and MPA are the two major forms of systemic vasculitis associated with ANCA [Hoffman 1998]. The incidence of these conditions in the United States is approximately

6,000 new cases per year, and the estimated prevalence is 25,000 to 30,000 [Watts 2015]. In a 20-year United States population-based study, the annual incidence of AAV was 3.3 per 100,000. The incidence rate of GPA was 1.3 and of MPA was 1.6. The overall prevalence of AAV was 42.1 per 100,000 [Berti 2017]. If untreated, AAV progresses from limited disease processes (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase, characterized by multiple complications of small-vessel vasculitis (i.e., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) [Reinhold-Keller 2000]. The outcome of untreated severe disease is death.

Although treatment failures and disease relapses decreased due to improvement of remission induction regimens during the last years, patients with MPA and GPA treated with conventional regimens have a nine-fold increased mortality risk in the first year attributed to infection, cardiovascular disease, malignancies, vasculitis activity, and renal disease [Flossmann 2011, Luqmani 2011]. It is proven that current therapies contribute more than half of this increased risk rather than the underlying disease itself [Little 2010]. Most of the side effects are contributed to the high dose of GCs which are still part of SOC for MPA and GPA. GCs have long-term side effects such as osteoporosis, Cushing's syndrome, increased infection risk and risk of diabetes [Moghadam-Kia 2010, Charlier 2009, McGregor 2012, Goupil 2013] and progressive organ damage [Robson 2015].

It was demonstrated that C5a and C5b receptors are involved in the pathogenesis of AAV and C5a levels are increased in patients with AAV [Chen 2017, Furuta 2013, Halbwachs 2012, Kettritz 2014]. Since IFX-1 is a monoclonal antibody, which specifically binds to the soluble human complement split product C5a, it is capable of a nearly complete blockade of C5a-induced biological effects while not affecting cleavage of C5 and formation of the complement MAC. Therefore, IFX-1 could be effective in the treatment of subjects with AAV and will be administered as add-on to SOC for AAV to improve the time to clinical remission.

In case of a lack of efficacy, subjects can receive other immunosuppressive therapy at the discretion of the investigator, or in case of a relapse after IMP treatment, subjects can receive adequate rescue medication as described in Section 7.3. Risk-limiting procedures are anticipated and therefore the hypothesized benefit of treatment with IFX-1 outweighs the potential risks for subjects participating in this study.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of the study is to investigate the safety and tolerability of two dose regimens of IFX-1 as add-on to SOC in subjects with GPA and MPA compared with placebo.

3.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To investigate the clinical response of two dose regimens of IFX-1 in subjects with GPA and MPA compared with placebo.
- To generate data for pharmacokinetic (PK) and pharmacodynamic (PD) modeling for two dose regimens of IFX-1.

All study endpoints are listed in Section 11.4.

4 STUDY DESIGN

4.1 OVERALL STUDY DESIGN AND PLAN

This is a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase II study. For each subject, the study will comprise a Screening Period (up to 2 weeks), a Treatment Period (Week 0 up to Week 16), and a Follow-up Period (after the IMP administration in Week 16 to Week 24). All subjects will receive the IMP, i.e., IFX-1 or placebo, from Week 0 to Week 16 and SOC throughout the whole study.

A total of 36 subjects are planned to be randomized to one of three treatment groups in a 1:1:1 ratio:

- Group A: 400 mg IFX-1 plus SOC
- Group B: 800 mg IFX-1 plus SOC
- Group C: placebo plus SOC

The IMP dosing schedule is presented in Table 1.

During the entire study, subjects will receive SOC at the discretion of the investigator as described in Section 6.2. The remission induction therapy used during the Remission Induction Phase normally comprise RTX or CYC and a standard dose of GCs. At the discretion of the investigator, subjects are allowed to switch to other SOC (AZA/MTX/MMF/MPS plus a standard dose of GCs) after clinical remission or to stay on RTX or CYC during the Remission Maintenance Phase. RTX or CYC plus intravenous GCs use can be started immediately after all screening assessments are performed, independent from the planned date of randomization. The recommended dose regimens for the SOC are described in Sections 6.2.1 to 6.2.6.

A PK substudy will be conducted in 15 subjects who provide additional consent for participation in this substudy. Subjects will be sequentially included for participation in the PK substudy, regardless of their assigned dose group if consent for participation is given.

4.2 NUMBER OF SUBJECTS AND STUDY SITES

This multicenter study is planned to be conducted at approximately 38 sites in the United States of America and Canada.

A total of 36 subjects (12 subjects per treatment group) will be randomized.

4.3 STUDY DURATION

The study start is defined as the date of the first screening visit of the first subject who signs informed consent, and the end of the study is defined as the date of the last visit of the last subject, as recorded in the electronic case report form (eCRF).

The study duration for an individual subject will be up to 26 weeks and will include the following study periods:

- Screening: up to 14 days before randomization (Week -2 to Week -1 [Day -14 to Day -1]).
- Treatment Period: starts in Week 0 (Day 1) and ends in Week 16 (Day 113).
- Follow-up Period: starts after administration of IMP in Week 16 (Day 113) and ends in Week 24 (Day 169).

IFX-1 or placebo will be administered during the total Treatment Period for a total of 11 infusions.

4.4 INDEPENDENT DATA MONITORING COMMITTEE

The safety of the subjects will be monitored by an unblinded IDMC. The IDMC will review the safety data of subjects who have completed the IMP administration in Week 16 and after subjects complete the Follow-up Period. The time points for the IDMC reviews will be defined in the IDMC charter. Safety analyses will be provided by an unblinded statistician.

4.5 PREMATURE TERMINATION OF THE STUDY

The study may be discontinued by the sponsor at any site in case any of the following criteria are met:

- The study protocol is not adequately adhered to (protocol deviations) despite training of the study site personnel.
- The data quality is deficient.
- The recruitment is inadequate.
- The IDMC recommends stopping the study for safety reasons.

Additionally, the entire study can be discontinued at all sites by the sponsor at any time for any reason (e.g., medical or ethical).

The investigator(s) will be notified in writing, outlining the reasons for discontinuation, and the investigator(s) must promptly inform all participating subjects. Detailed instructions on further assessments will be provided.

All study materials, except documents needed for archiving requirements, will be returned to the sponsor, including all records regarding the IMP. The clinical monitor will ensure that any outstanding data clarification issues and queries are resolved and that all study records at the study site are complete.

In accordance with applicable regulatory requirements, the sponsor will promptly inform the competent regulatory authorities of the discontinuation and its reason(s), and the investigator or sponsor will promptly inform the Ethics Committee.

The approval of the study can be rescinded, or the study can be discontinued by a competent authority or a responsible Ethics Committee.

5 STUDY POPULATION

5.1 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to a treatment group. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any non-treatment-emergent serious adverse event (SAE).

Rescreening of subjects who do not meet the criteria for participation in this study is not allowed.

5.2 INCLUSION CRITERIA

Subjects must meet all of the following criteria at Screening to be randomized into the study:

Inclusion Criteria	**Rationale**
1. Male or female, ≥18 years of age.	Safety concern
2. Written informed consent obtained from subject.	Administrative
3. Diagnosis of GPA or MPA according to the definitions of the Chapel Hill Consensus Conference (CHCC).	Effectiveness
4. Have at least one "major" item, or at least three (minor) other items, or at least two renal items on the Birmingham Vasculitis Activity Score (BVAS) Version 3.0.	Effectiveness
5. New or relapsed GPA or MPA that require treatment with CYC or RTX plus GCs.	Effectiveness
6. Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m^2.	Effectiveness
7. History of positive antigen-specific anti-neutrophil cytoplasmic antibody (ANCA) test through a documented positive ELISA test for either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) antibodies. For newly diagnosed subjects a recent positive ELISA testing for either anti-PR3 or anti-MPO is mandatory for inclusion.	Effectiveness

5.3 EXCLUSION CRITERIA

Subjects who fulfill any of the following criteria at Screening are not eligible to participate in the study:

Exclusion Criteria	**Rationale**
1. Any other multisystem autoimmune disease as listed in Appendix 18.4.	Safety concern
2. Requires mechanical ventilation because of alveolar hemorrhage at Screening.	Safety concern
3. Have required management of infections, as follows: a. Chronic infection requiring suppressive anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) b. Use of intravenous antibacterials, antivirals, anti-fungals, or anti-parasitic agents.	Safety concern
4. Known or suspected active drug and/or alcohol abuse.	Safety concern
5. Human immunodeficiency virus (HIV), hepatitis B, or hepatitis C viral screening test showing evidence of active or chronic viral infection at Screening or a documented history of HIV, hepatitis B, or hepatitis C.	Safety concern
6. One of the following abnormal laboratory findings at Screening: – White blood cells <3500/mm3 – Platelet count <120,000/mm3 – Total bilirubin >3 times the upper limit of normal (ULN) – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x ULN	Safety concern
7. Acute or chronic liver disease.	Safety concern
8. Known hypersensitivity to inactive ingredients of the GC capsules.	Effectiveness
9. History of or active malignancy, lymphoproliferative or myeloproliferative disorder. Individuals with squamous cell or basal cell carcinomas of the skin and individuals with cervical carcinoma in situ who have received curative surgical treatment may be eligible for this study.	Safety concern
10. History of anti-glomerular basement membrane (GBM) disease.	Safety concern

Exclusion Criteria	Rationale
11. Received CYC or RTX within 12 weeks before screening; if on AZA, MMF, MPS, or MTX at the time of Screening, these drugs must be withdrawn prior to receiving CYC or RTX.	Safety concern
12. Received more than 3 g cumulative dose of intravenous GCs within 4 weeks before screening.	Effectiveness
13. Received an oral daily dose of a GC of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening.	Safety concern
14. Received CD20 inhibitor, anti-tumor necrosis factor treatment, abatacept, alemtuzumab, any other experimental or biological therapy, intravenous immunoglobulin or plasma exchange, antithymocyte globulin, or required dialysis within 12 weeks before Screening.	Safety concern
15. Received a live vaccination within 4 weeks before Screening or planned between Screening and Week 24.	Safety concern
16. Subjects with a history of tuberculosis.	Safety concern
17. Pregnant or lactating.	Safety concern
18. Clinically significant abnormal electrocardiogram (ECG) during Screening, e.g., QTcF >450 ms.	Safety concern
19. Female subjects of childbearing potential unwilling or unable to use a highly effective method of contraception (pearl index <1%) such as complete sexual abstinence, combined oral contraceptive, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant, or depot contraceptive injection in combination with a second method of contraception such as condom, cervical cap, or diaphragm with spermicide during the study and for at least 4 weeks after last administration of IFX-1 (timeframes for SOC have to be considered as described in the respective Prescribing Information). Male subjects with female partners of childbearing potential unwilling to use contraception (condoms) during treatment and for at least 4 months after last administration of treatment.	Safety concern
20. Evidence or suspicion that the subject might not comply with the requirements of the study protocol.	Safety concern
21. Any other factor which, in the investigator's opinion, is likely to compromise the subject's ability to participate in the study.	Safety concern
22. The subject is an employee or direct relative of an employee at the study site or sponsor.	Administrative

Exclusion Criteria	Rationale
23. The subject is imprisoned or lawfully kept in an institution.	Administrative
24. The subject has participated in an investigational clinical study during the 12 weeks (or five times the half-life of the previous IMP, whichever is longer) before Screening, or plans to participate in another investigational clinical study during their participation in this study.	Administrative

5.4 DISCONTINUATION OF INDIVIDUAL SUBJECT PARTICIPATION

Each early discontinuation of individual subject participation, irrespective of the reason for discontinuation, must be documented by the investigator. If possible, the date, circumstances, and reason for discontinuation should be documented.

The investigator will attempt to complete all procedures usually required at the end of the study (i.e., Week 24) at the time when the subject's participation in the study is discontinued. Subjects who discontinue up to Week 16 will have a safety follow-up visit at 1 month (±3 days) after the last IMP administration.

5.4.1 Lack of Efficacy

In case of lack of efficacy, i.e., no improvement or deterioration in the BVAS since Screening, the investigator or subject can decide whether to discontinue from study participation.

5.4.2 Withdrawal of Informed Consent

Subjects may discontinue their participation in the study by withdrawing their consent at any time without giving reasons. Nevertheless, they should be asked about the reason(s) for discontinuation after being informed that they do not need to do so. Information as to when they withdrew consent must be documented.

Subjects are to be informed that when consent is withdrawn, the stored and captured data as well as blood samples taken until the time of termination may be used further to:

- Assess effects of the IMP being tested.
- Guarantee that the subject's personal interests are not adversely affected.
- Comply with the requirement to provide complete documentation when seeking marketing authorization.

5.4.3 Discontinuation of the Investigational Medicinal Product

Subjects must be discontinued from treatment with the IMP under any of the following circumstances:

- Unacceptable toxicity or TEAE, as determined by the investigator.
- Subjects unblinded for IMP administration due to safety concerns or emergency treatments.
- Non-compliance with study procedures or with IMP administration.
- Anaphylactic or other serious allergic reaction.
- Serious infection, including meningitis or sepsis.
- If, in the investigator's or sponsor's opinion, continued administration of IMP could be detrimental to the subject's well-being.
- In case of major relapse.
- Use of prohibited treatment that in the investigator's or sponsor's opinion necessitates the subject being removed.
- Biopsy confirmation of any malignancy.
- Pregnancy.

5.4.4 Lost to Follow-up

Lost to follow-up is defined as an unsuccessful attempt at contacting a subject.

At least three phone calls at three different times on consecutive days and a further phone call a week later should be performed. In case all calls are unsuccessful in contacting the subject, a certified letter will be issued to the subject. If the calls and the letter remain unanswered after approximately 1 month, the subject is to be declared as lost to follow-up. All the attempts at contacting the subject should be documented in the subject's records.

The date of being lost to follow-up is defined as the last date with any assessment of the subject.

6 STUDY TREATMENTS

6.1 DETAILS OF THE INVESTIGATIONAL MEDICINAL PRODUCT

6.1.1 Description of the Investigational Medicinal Product

Both IFX-1 and placebo are considered IMP.

IFX-1 is a monoclonal anti-human C5a immunoglobulin as active pharmaceutical ingredient, which is formulated in a phosphate buffered saline and Polysorbate 80. IFX-1 will be supplied in 10 mL glass vials at a concentration of 10 mg/mL (i.e., 100 mg per vial) for intravenous administration and will have the following composition:

Ingredient	**Strength**
IFX-1	10 mg/mL
Sodium chloride	150 mM
Sodium phosphate	10 mM
Polysorbate 80	0.05%

Placebo will be supplied in 10 mL glass vials for intravenous administration and will have the following composition:

Ingredient	**Strength**
Sodium chloride	150 mM
Sodium phosphate	10 mM
Polysorbate 80	0.05%

The placebo vials and content will have the same appearance as the IFX-1 vials.

6.1.2 Packaging and Labeling

The IMP will be packaged in cardboard boxes and labeled in accordance with all legal requirements. Each cardboard box will contain four vials of IFX-1 or placebo.

The cardboard boxes will be labeled with a unique number ("medcode"). The glass vials containing the IMP will be labeled with the same medcode as the cardboard boxes in which they are packed. Each cardboard box and each vial will be labeled with a multilingual booklet label or a specific single panel label. The labels are part of the Clinical Trial Application documentation.

6.1.3 Shipment

The IMP will be supplied to study sites by a Contract Manufacturing Organization (CMO) on behalf of the sponsor; the CMO will provide the initial and all subsequent supplies.

IMP availability on site will be triggered by an Interactive Web Response System (IWRS) ensuring continuous treatment of study subjects (for details refer to the IWRS Project Scope and Management document).

The IMP must be shipped at a temperature of 2°C to 8°C (35.6°F to 46.4°F) and should not be frozen. Each shipment will be controlled by a temperature logger, of which a read-out must be obtained by the site personnel upon receipt of the shipment.

Furthermore, the site personnel will check the IMP shipments for any loss, damage, or tampering and confirm receipt to the CMO. Records of the receipt of the IMP will be maintained by the site.

Any technical complaints arising from defects in the quality of the IMP, or defects in the packaging or labeling of the IMP must be reported to the CMO immediately, and the affected IMP must not be used.

If the shipping temperature is within the specified range, as confirmed by the temperature logger read-out and the receipt documentation, the CMO will release the IMP for use at the site via immediate notification from the IWRS. In the case of any deviation in the shipping temperatures, the notification for IMP release or rejection will be sent within a maximum of 24 hours.

The site personnel will be responsible for adequate handling and accountability of the IMP at the study site. Further details on adequate handling of the IMP will be provided in the Pharmacy Manual.

6.1.4 Storage

The IMP must be stored at 2°C to 8°C (35.6°F to 46.4°F) and should not be frozen. All IMP supplies must be stored separately from normal hospital inventories in a locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization (CRO) and the site personnel will maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported to the CMO. Further information will be provided in the Pharmacy Manual.

6.1.5 Drug Accountability

During the study, all vials of IMP will be reconciled against the current inventory and the dispensing records as a component of the monitoring visits. Data on the administration of the IMP kept at the site will be monitored throughout the study by the study monitor. Used vials can be destroyed at the site according to institutional policy and in compliance with the current applicable regulatory requirements after drug accountability has been assessed by the study monitor. If an institutional policy prevents used vials from being retained for monitors' review (e.g. institution must destroy used vials immediately), the institution must have an adequate drug accountability process and documentation for study monitors' review. The destruction of any unused vials of the IMP at the study site must be documented in a form provided by the CRO.

After completion of the study, copies of all IMP accountability records will be provided to the CRO. Further details on the monitoring procedures will be provided in a Monitoring Manual.

6.1.6 Reconstitution of IFX-1

The IMP will be reconstituted for infusion in a blinded manner at the study site or at the study site's pharmacy. The reconstituted IMP should be used within 4 hours after dilution when stored at room temperature. Otherwise, the reconstituted IMP has to be stored at 2°C to 8°C (35.6°F to 46.4°F) and used within 24 hours. Details on reconstituting the IMP will be provided in the Pharmacy Manual.

6.1.7 Administration

The IMP will be administered according to the dosing schedule in Table 1. Subjects will receive four administrations during the first 2 weeks and once every 2 weeks thereafter until Week 16.

Table 1 Dosing Schedule for IFX-1 and Placebo

	IFX-1 dose (in mg)										
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Week	**W0**	**W0**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**
Day	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**
Group A (400 mg IFX-1)	400	400	400	400	400	400	400	400	400	400	400
Group B (800 mg IFX-1)	800	800	800	800	800	800	800	800	800	800	800
Group C (placebo)	0	0	0	0	0	0	0	0	0	0	0

The IMP will be administered by the responsible personnel at the site as follows:

- The reconstituted IMP will be infused over a period of 30 to 60 minutes (±10 minutes) and as described in the Pharmacy Manual.
- At the end of the infusion, the intravenous line will briefly be flushed with approximately 10 mL of sterile sodium chloride (NaCl) to ensure that any IMP remaining in the line is administered.

Subjects should remain at the study site for at least 30 minutes after the end of the IMP administration; appropriate treatment for potential infusion-related reactions must be available during this time.

Each administration of IMP will be recorded in detail in the source data for the subject and eCRF.

If the scheduled infusion cannot be administered at the scheduled time (also considering an acceptable time window of ±1 day during the Treatment Period), the medical monitor should be informed. It will be decided on a case-by-case basis whether the IMP may be administered at a later time point or whether it should be omitted.

Further details of the IMP administration will be outlined in the Pharmacy Manual.

6.2 DETAILS OF THE STANDARD OF CARE

The immunosuppressive therapies taken or administered during the study (RTX, CYC, AZA, MTX, MMF, MPS, and GCs) are all considered SOC and will not be provided by the sponsor. The investigator should follow standard safety laboratory procedures according to the current United States Product Information.

All subjects will receive RTX or CYC plus GCs from Week 0 up to clinical remission (Remission Induction Phase). Following clinical remission and up to Week 24, subjects are allowed to switch to other SOC (AZA, MTX, MMF, or MPS plus GCs), to use throughout the remainder of the study, or to stay on RTX or CYC (Remission Maintenance Phase).

Administration of RTX or CYC plus intravenous GCs can be started immediately after all screening assessments are performed, independent from the planned date of randomization.

During the Screening period subjects can take up to 60 mg/day oral prednisolone (or equivalent). From Day 1 oral GCs must be used according to the standardized tapering schedule presented in Table 5.

6.2.1 Rituximab

RTX can be administered during the entire study. For further details on GC administration see Section 6.2.3.

RTX is a genetically engineered chimeric murine/human monoclonal immunoglobulin (Ig)G_1 kappa antibody directed against the CD20 antigen. Further details on RTX used for the treatment of GPA and MPA are summarized in Table 2.

Table 2 Summary of Clinical Data on Rituximab for Use in GPA/MPA

Indication	Treatment of GPA and MPA in adult patients in combination with GCs. Other indications: • Treatment of non-Hodgkin's lymphoma. • Treatment of chronic lymphocytic leukemia. • Treatment of rheumatoid arthritis.
Contraindications	None
Warnings and precautions	• Risk of severe, including fatal, infusion-related reactions typically during the first infusion of RTX with time to onset of 30 to 120 minutes. Premedication may reduce the incidence and/or the severity of infusion reactions. • Risk of severe, including fatal, mucocutaneous reactions with variable time of onset. • Risk of hepatitis B reactivation among subjects positive for hepatitis B surface antigen or hepatitis B core antibody. • Risk of cardiovascular adverse reactions. RTX infusions should be discontinued in patients with serious or life-threatening cardiac arrhythmias. • The use of live vaccines should be avoided. • RTX can cause neonatal harm and use in pregnancy should be avoided.

Dosage and administration	A dose of 375 mg/m^2 in combination with GCs (once per day) once weekly for 4 weeks as an intravenous infusion (independent of IFX-1). The use of RTX and/or intravenous GCs may only be started after all screening assessments have been completed. Same day infusions of intravenous GCs and RTX are permitted.

GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; RTX = rituximab
Source: Prescribing Information for rituximab.

6.2.2 Cyclophosphamide

CYC can be administered during the entire study. If used during the first 12 weeks of the Treatment Period, it can be administered according to the pulse regimen in Table 3. If CYC and IFX-1 or placebo are administered on the same day, the IMP should be administered before the CYC treatment.

Table 3 Pulse Regimen of Cyclophosphamide

Time [a]	Pulse Number [b]	Dosage and Route [c]
Week 0	1	15 mg/kg intravenously
Week 2	2	15 mg/kg intravenously
Week 4	3	15 mg/kg intravenously
Week 7	4	15 mg/kg intravenously
Week 10	5	15 mg/kg intravenously

a The first three pulses can be given at intervals of 2 weeks and can be given intravenously.
b This regimen implies clinical remission within 3 months.
c Cyclosphosphamide dose reduction indicated for subjects with creatinine values of 300 to 500 µmol/L.

CYC as alkylating drug is used off-label for treating patients with AAV. A summary of relevant details from the United States Prescribing Information on CYC is provided in Table 4.

Table 4 Summary of Clinical Data on Cyclophosphamide

Indication(s)	• Treatment of malignant lymphomas. • Treatment of minimal change nephrotic syndrome in pediatric patients not responding or not tolerating adrenocorticosteroid therapy.
Contraindications	• Hypersensitivity to CYC. • Urinary outflow obstruction.
Warnings and precautions	• Risk of myelosuppression, bone marrow failure, and severe immunosuppression. CYC should not be given to subjects with neutrophils ≤1,500/mm3 and platelets <50,000/mm3. • Latent infections can be reactivated. CYC treatment may not be indicated, or should be interrupted, or the dose reduced, in subjects who have or who develop a serious infection. • Urinary tract obstructions should be corrected before starting CYC therapy or, if not possible, patients excluded from therapy, because of the risk of hemorrhagic cystitis, pyelitis, ureteritis, hematuria, and urotoxicity. • CYC should be administered with caution in patients with risk factors for cardiotoxicity or pre-existing cardiac disease. • Risk of pulmonary toxicity leading to respiratory failure as well as late onset pneumonitis. • CYC is genotoxic and carries a risk of secondary malignancies. • Risk of veno-occlusive liver disease. • CYC interferes with oogenesis and spermatogenesis and may irreversibly impair male and female reproductive function and fertility. • May interfere with normal wound healing. • CYC can cause fetal harm and should be avoided during pregnancy. • Risk of hyponatremia associated with increased total body weight, acute water intoxication, and a syndrome resembling the syndrome of inappropriate secretion of antidiuretic hormone.
Dosage and administration	See Table 3 for the pulse regimen administered during the study.

CYC = cyclophosphamide
Source: Prescribing Information for cyclophosphamide.

6.2.3 Glucocorticoids

GCs are a class of corticosteroids and are used as anti-inflammatory agents with a wide range of indications. In patients with AAV, GCs are used off-label. GCs have to be

administered according to the tapering schedule presented in Table 5. For major side effects associated with oral GC therapy see Appendix 18.2.

Table 5 Standardized Dosing Schedule for Glucocorticoid Tapering

Time	Dose in mg (daily dose per week)
Week 0	60
Week 1	50
Week 2	40
Week 3	40
Weeks 4, 5	30
Weeks 6, 7	30
Weeks 8, 9, 10, 11	25
Weeks 12, 13	20
Weeks 14, 15	15
Weeks 16, 17, 18, 19	10
Weeks 20, 21, 22, 23	5
Weeks 24	0

6.2.4 Azathioprine

Subjects may be switched from RTX or CYC plus GCs to AZA at the investigator's discretion only during the Remission Maintenance Phase.

AZA is an immunosuppressive purine antimetabolite and is used off-label for treating patients with AAV. A summary of relevant details from the United States Prescribing Information on AZA is provided in Table 6.

Table 6 Summary of Clinical Data on Azathioprine

Indications	• Add-on therapy for the prevention of rejection in renal homotransplantations. • Treatment of active rheumatoid arthritis.
Contraindications	• Hypersensitivity to AZA. • Rheumatoid arthritis previously treated with alkylating agents.
Warnings and precautions	• Risk of lymphomas and other malignancies, particularly of the skin. Exposure to sunlight and ultraviolet light should be limited. • Risk of severe leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia. Severe bone marrow suppression may occur. Hematologic toxicities are dose-related and delayed hematologic suppression may occur. Patients with low to intermediate or absent thiopurine S-methyl transferase activity may be at increased risk of myelotoxicity. Genotyping or phenotyping for thiopurine S-methyl transferase activity is advisable. • Risk of developing serious infections. • AZA impaired male fertility in animals. No data are available in humans. • Risk of developing symptoms of gastrointestinal toxicity during the first several weeks of treatment. • AZA can cause fetal harm and should be avoided during pregnancy.
Dosage and administration	AZA can be administered at a dose of 2 mg/kg/day up to a maximum dose of 200 mg. If the subject is older than 60 years, the dose can be reduced by 25% and in subjects older than 70 years, a reduction of 50% is recommended.

AZA = azathioprine
Source: Prescribing Information for azathioprine.

6.2.5 Methotrexate

Subjects may be switched from RTX or CYC plus GCs to MTX at the investigator's discretion only during the Remission Maintenance Phase.

MTX is an antimetabolite that inhibits dihydrofolic acid reductase and is used off-label for treating patients with AAV. A summary of relevant details from the United States Prescribing Information on MTX is provided in Table 7.

Table 7 Summary of Clinical Data on Methotrexate

Indications	• Treatment of neoplastic diseases either alone or in combination with other anticancer agents. • Symptomatic control of severe, recalcitrant, disabling psoriasis confirmed by biopsy and/or dermatologic consultation and that is not adequately responsive to other forms of therapy. • Management of rheumatoid arthritis including polyarticular-course juvenile rheumatoid arthritis if patients are insufficiently responding or are intolerant to first-line therapy.
Contraindications	• Pregnancy (can cause fetal deaths or teratogenic effects) and lactation (excreted in human milk). • Alcoholism, alcoholic liver disease or other chronic liver disease. • Overt or laboratory evidence of immunodeficiency syndrome. • Pre-existing blood dyscrasias. • Hypersensitivity to MTX.
Warnings and precautions	• Potential for serious toxicity at any time of the therapy. • Due to diminished hepatic and renal function as well as decreased folate stores in older patients, relatively low doses should be considered. • Patients should be monitored closely for bone marrow, liver, lung, and kidney toxicities. • Diarrhea and ulcerative stomatitis require interruption of therapy. • Risk of developing malignant lymphomas in patients with low-dose MTX, which may regress following withdrawal of MTX. • Risk of severe, occasionally fatal, skin reactions within days of MTX treatment. Recovery of non-fatal reactions upon discontinuation of therapy. • Risk of opportunistic infections, especially Pneumocystis carinii pneumonia. • Increase risk of soft tissue necrosis and osteonecrosis when given concomitantly with radiotherapy.
Dosage and administration	MTX can be administered as tablets or subcutaneous injection up to a maximum dose of 25 mg/week, if the estimated glomerular filtration rate is ≤50 mL/min. Oral doses at 20 mg per week or higher can be administered as a split dose over 24 hours to ensure absorption.

MTX = methotrexate
Source: Prescribing Information for methotrexate tablets and injection.

6.2.6 Mycophenolate Mofetil and Mycophenolate Sodium

Subjects may be switched from RTX or CYC plus GCs to MMF or MPS at the investigator's discretion only during the Remission Maintenance Phase.

MMF and MPS are uncompetitive and reversible inhibitors of inosine monophosphate dehydrogenase and are used off-label for treating patients with AAV. A summary of relevant details from the United States Prescribing Information on MMF and MPS is provided in Table 8.

Table 8 Summary of Clinical Data on Mycophenolate Mofetil and Mycophenolate Sodium

	MMF	MPS
Indication(s)	• Prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.	• Prophylaxis of organ rejection in adult patients receiving a kidney transplant. • Prophylaxis of organ rejection in children ≥5 years of age who are at least 6 months post kidney transplant.
Contraindications	• Hypersensitivity to MMF, mycophenolic acid or any other component of the drug.	• Hypersensitivity to MPS, mycophenolic acid, MMF, or any other component of the drug.
Warnings and precautions	• Risk of increased susceptibility to bacterial, viral, fungal, and protozoal as well as new or reactivated viral including opportunistic infections. These infections may become serious. • Risk of lymphoma and other malignancies, especially on the skin. Exposure to sunlight and ultraviolet light should be limited. • Use during pregnancy is associated with increased risk of pregnancy loss and congenital malformations. • Risk of progressive multifocal leukoencephalopathy in patients with immunosuppressant therapy and impairment of immune function. • Risk of neutropenia (absolute neutrophil count<1.3 x 103/μL). • Risk of pure red cell aplasia when used in combination with other immunosuppressive agents. • MMF or MPS should be administered with caution in patients with active serious digestive system disease. • MMF or MPS should be avoided in patients with rare hereditary deficiency in hypoxanthine-guanine phosphoribosyl-transferase. • Contains a source of phenylalanine and should be used with caution in patients with phenylketonuria. • Live vaccine use should be avoided.	
Dosage and administration	MMF can be taken orally, twice daily as tablets. Reduction in subjects with a creatinine clearance of less than 25 mL/min may be required. The drug intake will be started at 1 g per day and the dose increased to the target dose of 2 g per day, if tolerated. The dose can be increased to 3 g daily for those with a suboptimal response.	The recommended daily dose of MPS is 1440 mg (8 tablets of 180 mg each) to be taken as two separate doses of 720 mg each. The dose can be increased to 2160 mg/day.

MMF = mycophenolate mofetil; MPS = mycophenolate sodium

Source: Prescribing Information for mycophenolate mofetil.

6.3 RANDOMIZATION AND BLINDING

Subjects will be assigned to one of the three treatment groups by means of a computer generated randomization list implemented into the IWRS. At each study site, each new subject who qualifies for randomization into the study according to the inclusion and exclusion criteria will be assigned a number in ascending order, beginning with the lowest number available at the study site. This procedure must be adhered to throughout the study. Interaction with the automated system will be provided via web access to the IWRS.

The blind will be maintained throughout the Treatment and Follow-up Periods as applicable for all IMP administered or provided to the subjects. The label, weight, appearance, and handling of the IMP will not compromise the blind.

If required, the investigator will be provided with technical options and password information to selectively break the randomization code for an individual subject via web access.

Safety data for the IDMC analyses will be handled and analyzed by an independent unblinded statistician.

Emergency Identification of Investigational Medicinal Product

The IWRS will be programmed with instructions for breaking the blind. Any premature breaking of the blind should be confined to emergency cases in which knowledge of the IMP received is necessary, e.g., to be able to provide appropriate emergency medical treatment. Whenever possible, the investigator should contact the medical monitor of the responsible CRO before breaking the blind, unless this would delay the emergency treatment. Subject safety must always be the primary consideration when determining whether to break the blind.

If a subject's treatment assignment is unblinded, the medical monitor will receive an alert from the IWRS. The investigator must inform the medical monitor within 24 hours of breaking the blind and the subject will be discontinued from further participation in the study. The date and reason why the blind was broken must be provided by the investigator and recorded in the source documentation for the subject and in the eCRF, as applicable.

6.4 PROCEDURES IN CASE OF SPECIFIC SIDE EFFECTS

6.4.1 Specific Side Effects of IFX-1

[redacted]

If a side effect occurs or is suspected after administration of IMP, subjects must be closely monitored, and as applicable the side effect must be reported as an adverse event (AE) (Section 10). Any treatment deemed medically appropriate should be initiated.

In case of the following specific types of side effects, the procedures reported below must be applied.

Infections: because IFX-1 blocks C5a, there is a theoretical risk of an increased rate of infections. Therefore, the investigator (and other health care professionals who take care of the subjects) should be closely monitored for signs and symptoms of infections in general. In case a subject develops a clinical picture that is difficult to distinguish from invasive infection, routine blood cultures and early start of antibiotic treatment are recommended. In subjects with bacterial infection, depending on the severity of the infection, it is important that concomitant antibiotic therapy be administered during treatment with IFX-1 to ensure appropriate control of the source of the infection. The investigator should pay close attention to the choice of an appropriate broad spectrum antibiotic treatment according to applicable guidelines. The IMP can be interrupted or discontinued at the investigator's discretion. Any invasive infection must be reported as an adverse event of special interest (AESI) (Section 10.3).

Meningitis/Meningococcal Sepsis: in case of signs of meningitis at any time during the study, the subject must be closely monitored and the guidelines for treatment of meningitis should be followed [Tunkel 2017, Van de Beek 2016]. This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search for the focus of the infection (e.g., computed tomography or magnetic resonance tomography). The IMP should be interrupted immediately in case of signs and symptoms of meningitis and discontinued if meningitis is confirmed.

Infusion-Related Reactions/Anaphylactic Reactions and Acute Systemic Allergic Hypersensitivity: in case of any severe, acute systemic hypersensitivity reaction during or shortly after infusion of IFX-1, the infusion should be stopped immediately and the subject discontinued from further dosing. In such cases, subjects should be closely monitored for any changes in blood pressure, heart rate, metabolic conditions, or organ function, and appropriate measures should be taken to stabilize all vital signs. Fluid resuscitation may be needed, as well as vasopressor therapy or other measures to treat changes in blood pressure, vital signs, or metabolic conditions in general. In cases of emergency with immediate life-threatening potential such as cardiac arrest or similar life-threatening changes, appropriate cardiopulmonary resuscitation should be started

immediately according to applicable guidelines, or as established at the study sites through existing standard operating procedures or other algorithms for cardiopulmonary resuscitation according to current recommended resuscitation guidelines.

For any potential infusion-related event, the investigator should check for a potentially developing or existing anaphylactic reaction. In case an anaphylactic reaction is anticipated, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction as recommended by existing guidelines for the treatment of anaphylactic reactions or, if established at the study sites, according to available standard operating procedures or other algorithms.

For further details regarding the definition and management of anaphylaxis, please refer to the Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium (Hugh et al., 2006)

If the investigator abstains from further dosing the subject can be maintained in the study and can continue with study procedures as scheduled.

In case of an emergency or other situation in which it is medically imperative for the investigator to identify the IMP that a subject has received or is receiving, the procedure for emergency identification of IMP must be followed.

6.4.2 Overdose of IFX-1

The consequences of an overdose with IFX-1 are not known.

If overdosing of the IMP occurs or is suspected, subjects must be closely monitored for any symptoms. In case of any symptoms, treatment as deemed medically appropriate by the investigator should be initiated. Overdoses accompanied by adverse outcomes must be recorded as treatment-emergent adverse events (TEAEs).

7 PRIOR AND CONCOMITANT THERAPY

Any medication (including, but not limited to, over-the-counter or prescription medicines such as aspirin, antacids, vitamins, mineral supplements, and/or herbal supplements), vaccine or procedure (e.g., mechanical ventilation) that the subject received during the 3 months before or at Screening (prior therapy) or receives during the study (concomitant therapy) must be recorded in the source documentation and in the eCRF, with details on the reason for use, date(s) of administration (with start and end dates), and dosing information, including dose, route, and frequency of administration.

Any AAV therapy that the subjects received 1 year prior to study enrolment will be documented in the source and in the eCRF by verbatim name with start and end dates.

7.1 *RECOMMENDED* CONCOMITANT THERAPY

Osteoporosis prophylaxis

Treatment measures to prevent osteoporosis are to be administered at the discretion of the investigator.

Pneumocystis Carinii Pneumonia (PCP) Prophylaxis

It is recommended to prescribe treatment medication to prevent PCP. The treatment measures prescribed are at the discretion of the investigator, and can be applied as per local practice. For details refer to the current Product Information also, if applicable.

Permitted concomitant therapy are described in Sections 7.2 and 7.3; prohibited concomitant therapies are listed in Section 7.4.

7.2 *PERMITTED* GLUCOCORTICOID THERAPY

Inhaled and topical GCs can be used for subjects diagnosed with diseases other than AAV (for example: eczema, asthma, chronic obstructive pulmonary disease, eosinophilic esophagitis), or for subjects with large airway involvement of GPA as documented by bronchoscopy. Local injections of GCs into subglottic GPA lesions can be given. All use of topical or inhaled GCs must be documented accurately in the source documentation and in the concomitant medication section of the eCRF.

Subjects on an oral GC dose of more than 10 mg/day prednisone-equivalent for more than 6 weeks continuously before Screening or who have received more than 3 g cumulative dose of intravenous GCs within 4 weeks before Screening will not be randomized in this study.

Intravenous GCs may only be started after all screening assessments have been completed. Same day infusions of intravenous GCs as pre-medication prior to each infusion of RTX are permitted.

During the Screening period subjects can take up to 60 mg/day oral prednisolone (or equivalent). From Day 1 oral GCs must be used according to the standardized tapering schedule presented in Table 5.

If subjects are on oral GC treatment at a dose of 10 mg/day or less during the Screening period, this dose has to be stopped before Day 1. From Day 1, oral GCs must be used according to the standardized tapering schedule presented in Table 5.

7.3 RESCUE THERAPY

Rescue therapy will not be provided by the sponsor. The administration or receipt of rescue therapy does not necessarily discontinue the subject from IMP administration and study participation.

Severe Disease Flare (Major Relapse):

A severe disease flare is defined as having a BVAS >3 or experiencing one of the major BVAS items listed in Appendix 18.4 that requires treatment with other than permitted AAV therapy following clinical remission (BVAS = 0) in this study. Depending on the severity of a subject's presenting symptoms, as well as the clinical picture, the investigator will be allowed to prescribe a maximum of 1 g of methylprednisolone per day for up to 3 days. In addition, up to 1 mg/kg oral prednisolone (or equivalent) may be prescribed with a subsequent tapering schedule per the investigator´s discretion.

A subject experiencing a major relapse should discontinue study drug but stay in the study, receive treatment with standard of care, at the discretion of the investigator, and will continue with study procedures as scheduled.

If a subject with a major relapse was discontinued from the study by Week 16, a safety follow-up visit must be performed 1 month (± 3 days) after discontinuation.

Limited Disease Flare (Minor Relapse):

A limited disease flare is defined as any minor item defined for the BVAS (see Appendix 18.4) after clinical remission (BVAS = 0) in this study. At the discretion of the investigator, subjects experiencing a limited disease flare can receive, together with the standardized GC dosing schedule, up to 20 mg/day of GCs (prednisone-equivalent) that should be tapered down to the standardized tapering dose over 14 days.

A subject experiencing a minor relapse will stay in the study and will continue with study procedures as scheduled.

If a subject with a minor relapse was discontinued from the study by Week 16, a safety follow-up visit must be performed 1 month (± 3 days) after discontinuation.

7.4 PROHIBITED THERAPY

The following therapies are prohibited for all subjects during the study:

- Tumor necrosis factor inhibitor treatment (e.g., etanercept)
- Anti-CD20 therapies other than RTX
- Abatacept
- Alemtuzumab
- Any other experimental or biologic therapies
- Intravenous, intramuscular, or sub-cutaneous immunoglobulin
- Plasma exchange
- Antithymocyte globulin
- Live vaccines
- Renal dialysis
- Any other ***oral or iv***. GCs (except for those used as rescue therapy as described in Section 7.3)

If administration of any prohibited concomitant therapy becomes necessary during the study for medical reasons, the subject is to be discontinued from further IMP administration. (S)he can be maintained in the study and continue with study procedures as scheduled.

The investigator should contact the medical advisor of the sponsor's designed CRO or the sponsor if there are any questions regarding prior or concomitant therapy.

8 STUDY PROCEDURES AND VISIT SCHEDULE

The assessments to be performed at each visit are presented in the Schedule of Assessments. The visit schedule is applicable to all subjects in Groups A, B, and C. The assessments will be performed according to the methods described in Section 11.

8.1 SCREENING

Screening is the predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for randomization into the study.

The screening procedures will be conducted between Day -14 and Day -1 before randomization.

The investigator may pre-screen subjects for study inclusion and exclusion criteria without first obtaining written informed consent for participation in the current study on the basis of one or both of the following situations:

- Pre-existing data (e.g., for study inclusion and exclusion criteria, as available in medical records held by the investigator).
- Initial contact (e.g., routine visit, phone call) where only routine and/or non-study-specific questions are allowed.

After subjects have provided written informed consent, potentially eligible subjects will be assessed to determine if all inclusion criteria and no exclusion criteria are met. All subjects must provide written informed consent before any study-specific assessments or procedures are performed. If the subject fulfills all of the inclusion criteria, does not meet any of the exclusion criteria, and written informed consent is available, the subject will be randomized.

All randomized subjects will be issued a subject card with relevant contact details, including emergency contact details. Subjects will be instructed on the completion of the PROs by the investigator at Screening.

If the subject meets an exclusion criterion or another reason for non-inclusion in the study is given after obtaining informed consent, the subject will not be randomized and will be deemed a screen failure.

8.2 TREATMENT PERIOD

The Treatment Period will comprise Visits 2 to 12 (Weeks 0 to 16). All visits will have an accepted time window of ±1 day.

At each visit, the planned assessments will be performed predose, unless otherwise specified in the Schedule of Assessments.

If any subject is discontinued during the Treatment Period (i.e., until Week 16), the assessments planned for Week 24 should be performed as soon as possible and again at the safety follow-up visit (Section 8.4).

Only RTX or CYC plus GCs may be used as SOC during the Remission Induction Phase (i.e., until clinical remission). Subjects are allowed to switch to AZA, MTX, MMF, or MPS plus GCs after clinical remission, at the discretion of the investigator.

8.3 FOLLOW-UP PERIOD

The Follow-up Period will comprise Visits 13 to 14 (from after the IMP administration at Week 16 to Week 24). All visits will have an accepted time window of ±3 days.

If any subject is discontinued after Week 16 but before Week 24, the assessments planned for Week 24 should be performed as soon as possible.

RTX, CYC, AZA, MTX, MMF, or MPS plus GCs can be used as SOC during this period.

8.4 SAFETY FOLLOW-UP VISIT

This visit will only be performed for any subjects who discontinue the study during the Treatment Period (i.e., until Week 16). The visit will occur at 1 month (±3 days) after the last IMP administration and the same assessments as for Week 24 will be performed.

8.5 UNSCHEDULED VISIT

Unscheduled visits to the study site will be for subjects with major or minor relapses. The assessments specified in the Schedule of Assessments should be performed.

9 STUDY VARIABLES AND ASSESSMENT METHODS

9.1 STUDY SUBJECTS

9.1.1 Demographics and Baseline Characteristics

The following demographic data and baseline characteristics will be documented at Screening:

- Age
- Gender
- Race and ethnicity
- Body weight
- Height
- Smoking status

9.1.2 AAV Medical History

Widely accepted diagnostic criteria, as opposed to classification criteria or definitions, have not yet been developed for GPA and MPA. In 1994, the CHCC developed definitions for these vasculitides and some of their mimickers with a revision issued in 2013 [Jennette 2013]. These definitions, along with the American College of Rheumatology Criteria for the classification of vasculitides are useful in formulating the diagnostic criteria that will be applied to determine a subject's eligibility for this study (see Appendix 18.1) [Fries 1990].

The AAV medical history will be documented in terms of:

- Positive antigen-specific ANCA titer prior to screening (including the type and last date of positive ANCA lab test result) as evidenced by a positive ELISA test for antibodies to proteinase 3 or antibodies to myeloperoxidase
- Number of major relapses since diagnosis
- Date of most recent major relapse
- Date of AAV diagnosis
- Family history of AAV (first degree family pedigree)

9.1.3 General Medical History

A complete medical history for the 12 months prior to screening will be obtained from each subject at screening.

9.1.4 Prior and Concomitant Therapy

All prior and concomitant therapy will be documented, as described in Section 7.

9.2 EFFICACY

9.2.1 Efficacy Variables

Efficacy will be assessed on the basis of the following variables:

- BVAS
- Vasculitis Damage Index (VDI)
- Physician Global Assessment (PGA)
- Renal variables
- PRO: 36-item Short Form survey (SF-36)
- [redacted]

9.2.2 Methods of Assessing Efficacy Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.2.2.1 Birmingham Vasculitis Activity Score Version 3.0

The BVAS Version 3.0 is a validated instrument for the assessment of disease activity and response to treatment in AAV [Mukhtyar 2009].

The BVAS Version 3.0 form is a list of 56 items with a numerical weight attached to each item, and each organ system has a ceiling score. The form is divided into nine organ-based systems (i.e., general symptoms such as arthralgia, arthritis, and fever, plus involvement of eight major organ systems), with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis (Appendix 18.3). Each organ system has a ceiling score. These scores reflect the proportional importance of each manifestation and each organ system. Completion of the form provides a numerical score by using the Glossary and Scoring Rules for the BVAS (Appendix 18.4). Scoring ranges are higher when any of the features are new or worse. Creatinine levels can be scored at a subject's first assessment only. Higher scores indicate more severe disease. A decrease of >16 units is clinically meaningful.

In order to standardize the BVAS assessment in this study, all attempts should be made that the same investigator scores the subject at all visits, and all investigators performing the BVAS assessment have to participate in a dedicated training (either face-to-face or web-based) and receive a certification prior to screening any subject. This certified

training is required in order to use the forms properly. Training and/or training material as well as certification will be provided.

9.2.2.2 Vasculitis Damage Index

The VDI will be used to assess damage induced by GPA or MPA and by the treatment applied during this study. The VDI is a validated assessment tool divided into 11 organ systems. The scoring sheet is divided into 10 systems plus an 11th section for other items, mainly related to the effects of drugs. The VDI is used to record any condition that has occurred and lasted for at least 3 months since the start of vasculitis and refers to chronic damage whether or not it is related to vasculitis. It consists of 64 items selected by expert consensus as representative of the forms of damage developed by subjects with systemic vasculitis [Exley 1997]. Completion of the form provides a numerical score by summation of each damage (Appendix 18.6). Each item scores 1 point.

Three scores will be calculated for each subject:

- Total VDI score: the total number of items will be counted leading to a minimum score of 0 and a maximum score of 64
- System score: the extent of disease defined by the number of separate systems with at least 1 item score
- Critical damage score: the number of items of damage consistent with organ failure (as defined in the glossary)

In order to standardize the VDI assessment in this study, all attempts should be made that the same investigator scores the subject at all visits, all investigators performing the VDI scoring should conduct a dedicated training (either face-to-face or web-based) and receive a certification prior to screening any subject. This certified training is required in order to use the forms properly. Training and/or training material as well as certification will be provided.

9.2.2.3 Physician Global Assessment

The PGA scale is an 11-point scale derived from the BVAS for GPA to record the assessment of the overall disease activity of GPA or MPA (not including longstanding damage) within the previous 28 days [Stone 2001]. The rating ranges from 0 (remission) to 10 (maximum activity) (Appendix 18.7).

All attempts should be made to ensure that the same investigator scores the subject at all visits and when completing this assessment, the investigator should not be influenced by the presence of any accumulated damage, complication of treatment, social/emotional problems, or other issues not related to active GPA or MPA.

9.2.2.4 Renal Variables

Renal variables will be analyzed for both safety and efficacy and will be used to adapt the different therapies during the course of the study.

The renal variables to be analyzed in this study are listed in Table 9.

Table 9 Renal Variables

Variable	Urine	Serum	Calculation	Laboratory
Creatinine	X	X		Central
Total protein	X	X		Central
Microalbumin	X			Central
MCP-1	X			Central
[redacted]				
Urinary MCP-1:creatinine ratio			X	
UACR			X	
eGFR			X	

eGFR = estimated glomerular filtration rate; MCP = monocyte chemoattractant protein; UACR = urinary albumin:creatinine ratio

All derived ratios and the eGFR will be calculated at the time points when the respective single serum or urinary parameters are planned to be assessed.

. Instructions regarding the collection, processing, and shipping of samples for analysis of laboratory parameters (i.e., urinary and serum creatinine, [redacted] and urinary monocyte chemoattractant protein [MCP-1]) will be available in the Laboratory Manual provided by the responsible lab.

The eGFR will be calculated by the central laboratory according to the Modified Diet in Renal Disease equation:

$$eGFR = 175 \times (\text{serum creatinine, mg/dL})^{-1.154} \times (\text{age, years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$$ [Levey 1999].

9.2.2.5 36-Item Short Form Survey Version 2

The SF-36 version 2 is a subject-reported generic measurement of health status that has proven useful in studies of both general and specific populations, comparing the relative burden of diseases and the health benefits produced by different treatments [Ware 1998]. Inclusion of the SF-36 has become standard practice for almost all clinical studies and observational studies for most rheumatic diseases, including vasculitis [Merkel 2011].

The SF-36 consists of 36 questions from the following eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Appendix 18.8).

Each domain is directly transformed into a scale from 0 to 100 on the assumption that each question carries equal weight. A lower score indicates a poorer health status; a higher score indicates a better health status (i.e., a score of zero is equal to maximum disability and a score of 100 is equal to no disability). The eight domains are summarized to form two distinct higher-ordered clusters (physical health and mental health).

A paper version of the questionnaire will be provided and thoroughly explained to the subjects during their visits to the study site. To avoid bias in the subject's response, the subject has to complete the questionnaire at the study site before the study site personnel performs any other assessments.

The study site personnel will be responsible to enter the data from the completed SF-36 questionnaire into the eCRF in a timely manner; the original paper questionnaires will then be filed in the study records.

9.2.2.6 Anti-neutrophil Cytoplasmic Antibody Status

At screening, history of positive antigen-specific ANCA test as evidenced by a positive ELISA test of either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) antibodies is required to enroll a subject into the study.

The ANCA testing performed by the central laboratory during the study will comprise testing for PR3-ANCA and MPO-ANCA. Further details are provided in the Laboratory Manual.

9.3 SAFETY

9.3.1 Safety Variables

Safety will be assessed on the basis of the following variables:

- AEs
- Glucocorticoid toxicity index (GTI)
- Physical examination
- Vital signs
- ECG
- Laboratory safety parameters
- Renal variables
- Pregnancy test

- Serology: HIV, hepatitis B, and hepatitis C status at Screening
- Anti-GBM status at Screening
- Anti-drug antibody (ADA) status

9.3.2 Methods of Assessing Safety Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.3.2.1 Adverse Events

The incidence, severity, and causality of AEs will be assessed at every visit from signature of the informed consent form at Screening to the subject's last evaluation according to the procedures described in Section 10.

9.3.2.2 Glucocorticoid Toxicity Index

The GTI has two components: the composite GTI and a specific list. In a first evaluation, excellent reliability and validity was shown [Miloslavsky 2016]. The composite GTI serves as the primary instrument and is intended to capture common toxicities that are sensitive to differing cumulative GC doses over the period of a typical clinical study. Nine domains and 31 items are in the composite GTI and 11 items and 23 items are included in the specific list. When a specific list item will occur, the most severe corresponding item in the composite GTI should also be scored (see Appendix 18.9). The composite GTI should be scored on at least twice in this study in a 3-month interval, since it measures changes in GC toxicity. The bone domain is excluded since the study is shorter than 1 year in duration. Therefore, the total score can range from -35 to 400. Higher scores indicate greater GC toxicity, negative scores demonstrate improvement in GC toxicity. Further information will be provided in a specific manual. The laboratory assessments required for this index are part of the safety laboratory variables. As the GTI measures the changes in GC toxicities, only assessment of the specific list items are necessary on Day 1.

9.3.2.3 Physical Examinations

Physical examination findings that are related to the medical history will be recorded in the source documentation and in the eCRF.

Any abnormality noted after starting treatment with IMP (Day 1) will be evaluated by the investigator for whether it constitutes an AE.

9.3.2.4 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate (counted for at least 30 seconds after 5 minutes in a sitting position), respiratory rate, and body

temperature will be obtained at each visit. Blood pressure and pulse rate should be measured before blood samples are taken.

9.3.2.5 Electrocardiogram

If there are any clinically significant findings in the resting 12-lead ECG performed at Screening, the investigator must contact the medical monitor at the sponsor-designated CRO before randomizing the subject into the study.

An appropriately certified physician will interpret, sign, and date each ECG. Any clinically significant findings will be recorded in the source documentation and in the eCRF. Each signed, original ECG will be reviewed by the clinical monitor for correctness (date, time, and clinically relevant findings, if applicable) and stored with the source documentation at the study site.

9.3.2.6 Safety Laboratory

Blood samples for safety laboratory analysis should be obtained after the subjects have provided responses to questionnaires and after vital signs assessments have been performed, but before administration of IMP.

Analyses will be conducted by a certified central laboratory.

Instructions regarding the collection, processing, and shipping of samples for analysis of laboratory safety parameters will be available in the Laboratory Manual provided by the responsible lab. Instructions for urine pregnancy testing are also provided in the Laboratory Manual.

The following parameters will be assessed using standard validated methods:

Clinical chemistry:	serum creatinine, urea, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, total bilirubin, lactate dehydrogenase, alkaline phosphatase, sodium, potassium, calcium, total protein and albumin
Hematology:	red blood cells (erythrocytes), platelets, hemoglobin, white blood cells (including differential blood count), and complete blood count
Coagulation:	partial thromboplastin time and international normalized rate
For GTI:	glycosylated hemoglobin and low density lipoprotein

All abnormal laboratory values will require a comment in the eCRF according to the following classification:

- Not clinically significant

- Clinically significant
- Error (e.g., laboratory error, improper sample preparation, hemolysis, or delayed transit to laboratory)

At Screening, any laboratory value that deviates from the reference range and is considered by the investigator to be clinically significant, or considered as a result of a disease noted in the medical history, must be documented on the medical history page of the eCRF. Any deviation from the reference range considered by the investigator as clinically significant at any later visit must be documented in the eCRF as an AE if not previously documented as an ongoing medical condition or as an ongoing AE. Follow-up laboratory investigations due to an AE will be performed at a local laboratory at the discretion of the investigator.

Detailed instructions regarding the collection, processing, etc., of samples will be provided in the Laboratory Manual provided by the responsible lab.

9.3.2.7 Renal Variables

Renal variables will be measured as described in Section 9.2.2.4.

9.3.2.8 Pregnancy

Pregnancy testing will be conducted in all women of childbearing potential. A woman is considered to be of childbearing potential (i.e., fertile, following menarche and until becoming postmenopausal, unless permanently sterile). Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

The pregnancy test is to be performed in serum at Screening and Week 24/time of discontinuation (and safety follow-up for subjects who discontinue until Week 16) and in urine (using a dipstick) at the other visits indicated in the Schedule of Assessments.

If any pregnancy test is positive, the subject will not be eligible for participation, randomization, or continuation in the study.

Lactating women will not be eligible for participation or continuation in the study.

9.3.2.9 Serology

The following serology tests will be performed: HIV test and hepatitis B and C tests. Analyses for HIV-1 or HIV-2 antibodies will be conducted by the central laboratory.

Subjects will not be eligible for participation in the study if they test positive for HIV infection.

Analyses for the presence of hepatitis B infection will be conducted by a central laboratory using a hepatitis B DNA polymerase chain reaction test and a hepatitis B surface antigen test concurrently. If the result meets or exceeds detection sensitivity, the subjects will be excluded from participation in the study.

Analyses for the presence of anti-hepatitis C antibodies in serum will be conducted by a central laboratory via chemiluminescence.

Detailed instructions regarding the collection, processing, etc., of samples will be provided in the Laboratory Manual provided by the responsible lab.

9.3.2.10 Anti-Glomerular Basement Membrane Disease Assessment

Subjects with a history of anti-glomerular basement membrane (anti-GBM) disease are not eligible for study participation. Blood samples taken at Screening will additionally be measured for anti-GBM using an immunoassay to assess the anti-GBM status.

Detailed instructions regarding the collection, processing, etc., of samples will be provided in the Laboratory Manual provided by the responsible CRO.

9.3.2.11 Anti-Drug Antibodies

Retention samples will also be collected for possible future analysis.

ADAs will be measured in serum samples at a specialized laboratory using a validated homogeneous electrochemiluminescence-based bridging assay for initial detection as well as an additional confirmatory assay in case of positive findings detected in the initial test. Samples that are confirmed as ADA-positive will be quasi-quantified by titration.

Detailed instructions regarding the collection, processing, etc., of samples will be included in the Laboratory Manual provided by the responsible lab.

9.4 PHARMACOKINETICS, PHARMACODYNMICS, AND BIOMARKERS

9.4.1 Variables

PK will be assessed by measuring the IFX-1 concentration in plasma.

PD will be assessed by measuring: C5a, and IFX-1 blocking activity.

Biomarkers will be assessed by measuring: 50% hemolytic complement (CH50), C-reactive protein (CRP), [redacted].

9.4.2 Methods of Assessing Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.4.2.1 Pharmacokinetics

[redacted]

Serial PK blood samples will only be collected from 15 subjects, who provide additional consent to participate in the PK substudy. [redacted]

[redacted]

9.4.2.2 Pharmacodynamics

Instructions regarding the collection, processing, and shipping of samples to the central laboratory will be available in the Laboratory Manual provided by the responsible lab.

Table 10 Pharmacodynamic Variables

Variable	[redacted]	Laboratory
C5a	[redacted]	Specialized
IFX-1 blocking activity	[redacted]	Specialized

9.4.2.3 Biomarkers

Instructions regarding the collection, processing, and shipping of samples to the central laboratory will be available in the Laboratory Manual provided by the responsible lab.

Table 11 Biomarker Variables

Variable	Matrix	Laboratory
CH50	Serum	Central
[redacted]	[redacted]	[redacted]
CRP	Serum	Central
[redacted]	[redacted]	[redacted]

CH50 = 50% hemolytic complement; CRP = C-reactive protein; [redacted]

[redacted]

10 ADVERSE EVENT REPORTING

10.1 ADVERSE EVENTS

10.1.1 Definition

An AE is any untoward medical occurrence in a subject administered an IMP; an AE does not necessarily have to have a causal relationship with the treatment.

AEs encompass any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that arises or worsens after the inclusion of the subject into the study.

"Lack of efficacy" and "Failure of the expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE.

AEs may include:

- The significant worsening of the disease or symptoms of the disease under investigation following administration of an IMP.
- Illnesses that coincide with an onset after administration of an IMP.
- Exacerbation (i.e., increase in frequency or severity) of a pre-existing condition. Chronic illnesses present prior to study entry, other than the indication being investigated, should be recorded in the medical history page of the eCRF and only be reported as AEs if there is an increase in the frequency or severity of the condition during the study.
- For laboratory safety parameters, any absolute values outside of the reference range or changes after initial administration of the IMP that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs if not previously documented as ongoing medical conditions or as ongoing AEs. Examples of laboratory abnormalities that should be considered as AEs include those that result in discontinuation of treatment with the IMP, withholding treatment with the IMP pending some investigational outcome, reduction of IMP dose, or additional concomitant therapy.
- Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE.

Laboratory findings do not need to be reported as AEs in the following cases:

- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (e.g., values that are incompatible with life).

- An abnormal laboratory value that cannot be confirmed after repeated analysis, preferably in the same laboratory (i.e., the previous result could be marked as not valid and should not necessarily be reported as an AE).

In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs, if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

AEs do not include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE.
- Untoward medical findings that occur before initial administration of the IMP if they occur in the scope of investigations that are performed for assessing inclusion and exclusion criteria (e.g., results of laboratory tests conducted at Screening).
- Situations where an untoward medical occurrence has not occurred, e.g., planned hospitalization due to a pre-existing condition that has not worsened, hospitalization that occurs for a procedure not associated with an AE (e.g., elective surgery or social admission), or hospitalization for a diagnostic procedure that takes less than 24 hours.
- Overdose of an IMP or any concomitant therapy that does not result in any adverse signs or symptoms. Details of the dosing (volume, location of infusion, and infusion rate) of the IMP will be recorded in the eCRF.
- Anticipated day-to day fluctuations of pre-existing disease(s) or condition(s) present at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, sign, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

At each visit to the study site, the investigator will determine whether any AEs have occurred. If known, the medical diagnosis of an AE should be recorded according to the listing of individual signs and symptoms.

10.1.2 Documentation and Reporting

The observation period for AEs will start with confirmation of signed written informed consent at Screening (i.e., at Day -14 to Day -1) and ends at Week 24.

All AEs reported from the time the subject gives written informed consent to participate in the study until 12 weeks after the last administration of IMP will be recorded, irrespective of whether they were solicited or reported spontaneously by the subject. AE information will be collected and recorded in the eCRF. For subjects who discontinue until Week 16, a safety follow-up visit will be performed 1 month ***(±3 days)*** after the early discontinuation.

Any AEs judged by the investigator to be at least possibly related to treatment with the IMP should be reported to the sponsor regardless of the length of time that has passed since the subject has completed the study.

Every attempt should be made to describe AEs in terms of a diagnosis. If appropriate, component symptoms should be listed in addition to the diagnosis. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses in the eCRF.

All subjects who experience AEs, irrespective of whether they are considered by the investigator to be at least possibly related to treatment with the IMP, must be monitored to determine the outcome. The clinical course of each AE will be followed up according to accepted standards of medical practice, even after the subject has completed participation in the study, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate the follow-up. Should the AE result in death, a full pathologist's report should be provided, if possible.

AEs will be classified according to their severity, causal relationship to the IMPs, and seriousness.

If the severity of a recurrent AE changes from mild to moderate, from moderate to severe, or from mild to severe, this AEs recurrence should be reported as a new AE.

If the AE is serious or of special interest, as defined in Sections 10.2.1 and 10.3, the investigator or other authorized medical personnel at the study site must be notified and complete the paper "SAE form" at the time the SAE is detected. SAE reporting should occur within 24 hours (Section 10.2.2).

Severity of Adverse Events

The severity of AEs will be assessed according to the following criteria:

Mild	• Transient or mild discomfort • No limitation in activity • No medical intervention or therapy required
Moderate	• Marked limitation in activity • Some assistance usually required • Medical intervention or therapy required • Hospitalization possible

Severe	• Extreme limitation in activity • Significant assistance required • Significant medical intervention or therapy required • Hospitalization or hospice care probable

Causal Relationship of Adverse Events

The investigator must assess whether or not the AE is causally related to administration of the IMP. Even if the investigator considers that there is no causal relationship to the IMP, the AE must still be reported.

The causal relationship of AEs to administration of the IMP will be assessed according to the following criteria:

Not related	• Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship impossible • Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically) • Has occurred before administration of the IMP in comparable severity and/or frequency
Unlikely related	• Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Possibly related	• Event or laboratory test abnormality with reasonable time relationship to administration of the IMP • Could also be explained by disease or other drugs • Information on IMP withdrawal may be lacking or unclear
Probably related	• Event or laboratory test abnormality with reasonable time relationship to administration of the IMP • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required

Certainly related	• Event or laboratory test abnormality with plausible time relationship to administration of the IMP • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically or pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary

All AEs classified as "possibly", "probably", or "certainly" related will be considered as "at least possibly related to the IMP". All AEs classified as "not related" or "unlikely related" will be considered as "not related" to the IMP.

The degree of certainty with which an AE is attributed to administration of the IMP or an alternative cause (e.g., natural history of the underlying disease, concomitant therapy**,** AxMP etc) must be determined on the basis of how well the AE can be understood in terms of:

- Known pharmacology of the IMP
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product-related (e.g., headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (e.g., the event being related by time to administration or termination of treatment with the IMP, drug withdrawal, or reproduced on rechallenge)

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definition

An AE is defined as serious (i.e., as an SAE) according to the ICH E2A guideline if any of the following criteria are fulfilled:

- Results in death
- Is life-threatening

  NOTE: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The following hospitalizations are not considered to be serious AEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalization for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed after administration of IMP)

10.2.2 Documentation and Reporting

The observation period for SAEs starts with confirmation of signed written informed consent at Screening (i.e., at Day -14 to Day -1) and ends at Week 24.

Any SAE judged by the investigator to be at least possibly related to treatment with the IMP should be reported to the sponsor regardless of the length of time that has passed since study completion.

SAEs have to be documented on "SAE forms" and the investigator must report them immediately to the CRO, or no later than 24 hours after becoming aware of the SAE. If more information about the SAE becomes available later, this must also be reported immediately or no later than 24 hours after becoming aware of the SAE.

In case of a subject's death, the investigator will provide the applicable Ethics Committee(s) and the applicable responsible authorities with any further information requested.

In all reports, personal data are to be anonymized by using the subject identification number. It must be possible to relate the initial and all follow-up reports to each other by means of the subject identification number, or name and address, or the like.

The investigator must report all SAEs to the following contact details:

Fax: [redacted]

[redacted]

10.3 ADVERSE EVENTS OF SPECIAL INTEREST

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it.

For this study, the following AEs are defined as AESIs:

- Infusion-related reactions/anaphylactic reactions and ~~A~~acute systemic hypersensitivity reaction during or shortly after IFX-1 infusion.
- Meningitis
- Meningococcal septicemia
- Invasive infection

[redacted]

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

10.4.1 Definition

Suspected unexpected serious adverse reactions (SUSARs) are side effects whose nature or severity is inconsistent with the information available about the product in the Investigator's Brochure.

10.4.2 Documentation and Reporting

The sponsor will submit all available information on a SUSAR immediately to the applicable Ethics Committee, the applicable regulatory authority, and the investigators in this study, at the latest within 15 calendar days after the event becomes known.

For every SUSAR that results in death or a life-threatening condition, the responsible Ethics Committee, the applicable regulatory authority, and the investigators in this study must be informed by the sponsor within 7 calendar days after the event becomes known. Additional information has to be given within 8 further calendar days.

10.5 PREGNANCY

Pregnancy, by definition, is not considered as an AE unless it results in a complication (such as a maternal complication during pregnancy) that meets the definition of an AE, results in spontaneous abortion or stillbirth, or is associated with a congenital anomaly or birth defect in the fetus. Any such complication must then be reported accordingly as an SAE.

A female subject who becomes pregnant while participating in the study, or up to and including 28 days after the last dose of IMP, must notify the investigator immediately and must discontinue treatment with the IMP. The subject may continue other study procedures at the discretion of the investigator.

The sponsor and the designee of the sponsor must be notified within 5 days of the investigator becoming aware of the pregnancy, using the following contact details:

Fax: [redacted]
[redacted]

Whenever possible, a pregnancy in subjects exposed to IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator.

In certain situations, it may be necessary to monitor the development of the child for an appropriate period after birth. If this is the case, details should be included in this section.

Severe side effects and complications during a pregnancy as well as congenital birth defects are SAEs per definition and, therefore, have to be reported additionally as SAEs according to the reporting procedures described above.

10.6 THERAPEUTIC PROCEDURES

If a subject requires treatment as a result of an AE/SAE, the treatment must meet the recognized standards of medical care in order to restore the subject's health. Appropriate resuscitation devices and medication must be available in order to treat the subject as quickly as possible in the event of an emergency.

The actions taken to treat the AE/SAE must be documented by the investigator either in the appropriate eCRF and/or using additional documents.

11 STATISTICS

11.1 GENERAL CONSIDERATIONS

A detailed statistical analysis plan will be developed and finalized before the final unblinding of the study database.

The statistical analysis plan will include the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report.

All endpoints and variables will be adequately evaluated. Individual data will be listed. Data will be summarized using suitable descriptive statistics. Data will be analyzed by treatment group and treatment period and might be further differentiated (e.g., by visit or by study site). [redacted]

11.2 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was performed for this study. A total of 36 subjects will be randomized in a ratio of 1:1:1 in the two active treatment groups and the placebo group. [redacted]

11.3 ANALYSIS SETS

Safety analysis set (SAF): the SAF will consist of all subjects who will receive at least one administration of the IMP (one infusion of IFX-1 or placebo).

Full analysis set (FAS): the FAS will consist of all subjects who will receive at least one administration of the IMP (one infusion of IFX-1 or placebo).

Safety analyses will be based on the SAF. Efficacy analyses will be provided for the FAS.

More detailed specifications of the analysis sets and analyses will be provided in the statistical analysis plan.

11.4 ENDPOINTS

11.4.1 Safety

11.4.1.1 Primary

The primary safety endpoint is:

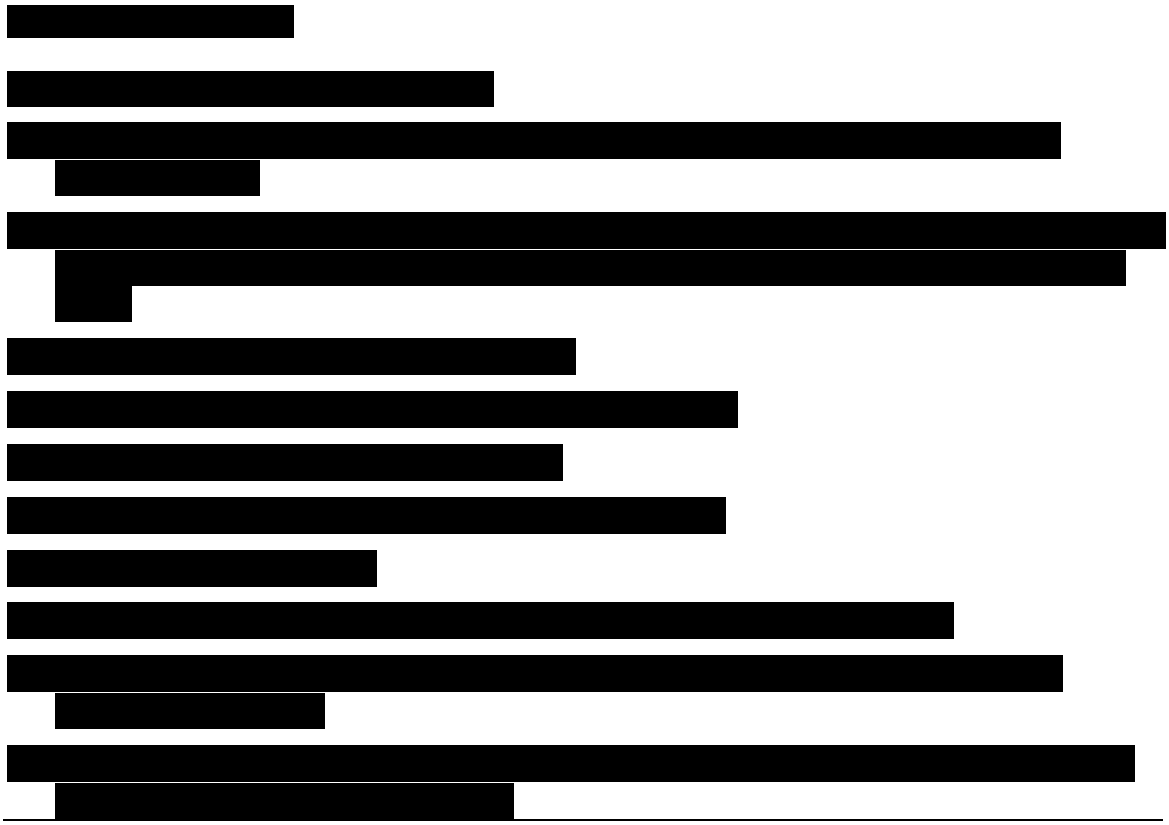
- Number and percentage of subjects who experience at least one TEAE per treatment group.

11.4.1.2 Secondary

The secondary safety endpoints are:

- IMP-related SAEs
- IMP-related TEAEs
- AESIs

For these secondary endpoints, the number of subjects and events by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term will be evaluated as well as the percentage of subjects who experience at least one AE in the respective category.



- [redacted]

[redacted]

11.4.2 Efficacy

The secondary efficacy endpoints are:

- Proportion of subjects achieving clinical response (defined as a reduction in BVAS of ≥50% and no worsening in any body system) at Week 16. Subjects who receive rescue medication for major relapse before Week 16 will be considered as not having achieved clinical response at each time point later than the first administration of rescue therapy.
- Proportion of subjects with clinical remission (BVAS = 0) at Week 16

[redacted]

- [redacted]

[redacted]

11.4.3 Quality of Life

The SF-36v2 will be analyzed by time point and changes from baseline will be determined per overall score, the physical component score (PCS), the mental component score (MCS), and per domain.

11.4.4 Pharmacokinetics

The secondary PK endpoints are:

- The exposure to IFX-1 in all subjects will be measured as the plasma concentration of IFX-1 determined on Day 1 and at all subsequent scheduled visits to the study site through Week 24, before administration of IMP, and in Weeks 1 (Day 4), 4, and 16 after administration of IMP using a separate infusion line. Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point.
- [redacted]

11.4.5 Pharmacodynamics

The PD of IFX-1 are primarily measured by plasma concentration of C5a and in addition by the IFX-1 blocking activity in plasma sample, which are determined at pre-specified times after administration of IFX-1. Plasma concentrations of C5a and IFX-1 blocking activities will be summarized by time point and as absolute and relative change from Day 1. [redacted]

11.4.6 Biomarkers

Serum concentrations of CRP, CH50 [redacted] will be summarized by time point and as absolute and relative change from Day 1.

11.5 ANALYSES OF ENDPOINTS

11.5.1 Safety

For all safety endpoints that represent a subset of all observed AEs (e.g., TEAEs, SAEs, AESIs) the number of events and the number and percentage of subjects who had at least one AE in the respective subset will be displayed overall and by MedDRA System Organ Class and Preferred Term stratified by treatment group as well as pooled for the IFX-1 treatment groups.

For the primary endpoint, the number and percentage of subjects with TEAEs will be further grouped by severity and causal relationship. Where AEs are grouped by severity or relationship, the maximum severity/relationship per subject and class of AE will be considered. If the number of subjects discontinuing treatment or the study prematurely is substantial, further analyses taking into account the time of AE onset and cumulative dose may be considered.

Continuous safety parameters, e.g., safety laboratory parameters or GTI, will be analyzed by time point and treatment group using descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, and upper quartile) for absolute values and absolute and relative changes from baseline, if applicable. Categorical safety parameters, such as the number of patients with proteinuria and/or hematuria, will be summarized by absolute and relative frequencies by time point and treatment group.

Shifts in safety laboratory parameters from normal at baseline to outside the normal ranges will be displayed additionally at each measured time point stratified by treatment group.

The number and percentage of subjects with anti-drug antibodies predose will be displayed at each measured time point by treatment group and pooled for the IFX-1 treatment groups.

11.5.2 Efficacy

Subjects who receive rescue medication for major relapse will be considered as not having achieved clinical remission at each time point later than the first administration of rescue medication.

Continuous efficacy parameters (e.g., BVAS) will be analyzed by descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, and upper quartile) for absolute values and changes from baseline (absolute and relative) by time point and treatment group. Additionally, the IFX-1 treatment groups will be pooled for the summary statistics.

Categorical efficacy parameters, such as the number of patients achieving clinical response, will be summarized by absolute and relative frequencies by time point and

treatment group. Additionally, absolute and relative frequencies will be displayed with the IFX-1 treatment groups pooled. The difference in the proportion of subjects with clinical response between the IFX-1 treatment groups (individually and pooled) as compared with the placebo group will be displayed along with its exact 90% confidence interval calculated according to the Agresti-Min method [Agresti 2001].

[redacted]

11.5.3 Quality of Life

Absolute values and changes from baseline in the overall SF-36 and per domain at Weeks 16 and 24 will be analyzed by descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline (absolute and relative) by time point and treatment group and pooled for the IFX-1 treatment groups.

11.5.4 Pharmacokinetics

Actual sampling times and IFX-1 plasma concentrations will be tabulated by subject. [redacted]

11.5.5 Pharmacodynamics

PD endpoints will be analyzed by time point and also as absolute and relative change from baseline, if applicable, at each time point using descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, and geometric mean) for each treatment group and pooled for the IFX-1 treatment groups

11.5.6 Biomarkers

Biomarkers will be analyzed by time point and also as absolute and relative change from baseline at each time point using descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, and geometric mean) for each treatment group and pooled for the IFX-1 treatment groups.

11.6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics and demographic information (including medical history and surgeries) will be summarized by treatment group and overall. If applicable, the baseline measurement will be defined as the latest measurement obtained prior to the first administration of IMP.

11.7 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant therapies will be summarized by absolute and relative frequencies by treatment group and overall. Therapies will be defined as concomitant if the start or end date is later than the date of first IMP administration, or if no end date is available (ongoing therapy).

In case of incomplete start and/or end dates, a therapy is considered as concomitant if it is possible that the therapy was administered after first dose of IMP (e.g., if only end year and month are provided and are equal to the month and year of the first IMP administration).

11.8 SUBJECT DISPOSITION

The disposition of subjects who were enrolled (i.e., signed the written informed consent form) in the study as well as reasons for discontinuation from study and treatment will be summarized for each group.

11.9 TREATMENT EXPOSURE

The administration of IMP will be summarized by time point and treatment group and will include the number and percentage of subjects completing each treatment visit and the mean dose per infusion at each visit. The actual received cumulative dose in mg and the dose relative to the planned cumulative dose will be calculated per subject and will be summarized for each treatment group.

11.10 HANDLING OF MISSING DATA

The missing value imputation will be defined in the Statistical Analysis Plan.

11.11 INTERIM ANALYSIS

No formal interim analysis will be performed.

An unblinded IDMC will review the safety data, as described in Section 14.3.

12 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

12.1 GOOD CLINICAL PRACTICE

All persons participating in the conduct of the study (e.g., sponsor, investigators) commit themselves to observe the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) as well as all pertinent national laws and the ICH guidelines for GCP (June 2017) and CPMP/ICH/135/95 (September 1997).

12.2 ETHICS COMMITTEE AND RESPONSIBLE REGULATORY AUTHORITY

The protocol and other associated documents will be submitted to the applicable Ethics Committee for approval. The study documents will be submitted to the applicable regulatory authority.

The study can only start after obtaining a positive evaluation by the applicable Ethics Committee and approval from the applicable regulatory authority. The written approval of the applicable Ethics Committee and the applicable responsible regulatory authority must be filed in the trial master file. Additionally, each study site must receive a copy of these documents to be filed in the investigator site file.

12.3 SUBJECTS INFORMATION AND INFORMED CONSENT

The investigator must explain to each potential study subject the nature of the study, the objectives, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. The potential subjects must be informed that participation in the study is voluntary, that they may withdraw their consent to participate at any time, and that withdrawal of consent will not affect the subsequent medical treatment of the study subject or the relationship to the treating physician.

The informed consent must be given by means of standard written statements, written in non-technical language. The subjects should read the informed consent form and consider their decision before signing and dating the document. A copy of the signed document must be given to the subject. No subject can be involved in the study if he/she is related to the investigator, any member of the team at the study site, or the sponsor.

The informed consent of the subject must also refer specifically to the assessment and processing of data on the subject's health. The subject is to be informed explicitly about the purpose and extent of the assessment and the use of their personal data, especially the health-related data. Informed consent for the storage of samples for possible future biomarkers testing and the PK substudy will also be given.

12.4 PROTOCOL AMENDMENTS

If modifications are made to the protocol, after it has been positively appraised by the Ethics Committee and approved by the responsible regulatory authority, these modifications must be reappraised and approved by the Ethics Committee and the responsible regulatory authority if the changes:

- Are such that they may affect the subjects' safety
- Are fundamental to the therapeutic procedures
- Result in further data collection that necessitates changes to the subject information and/or informed consent form
- Affect the interpretation of the scientific documents upon which the study is based or the significance of the results of the study
- Significantly affect the leadership or conduct of the study
- Concern the quality or the innocuousness of the investigational drug

Protocol amendments need the authorization of the sponsor, the coordinating investigator, and the responsible biostatistician, if applicable. All protocol amendments will be:

- Submitted to the Ethics Committee and, where applicable, to the responsible regulatory authority
- Provided in written form to the responsible parties
- Filed in the trial master file

13 DOCUMENTATION

13.1 ELECTRONIC CASE REPORT FORMS

All data assessments required by this clinical study protocol will be collected in an eCRF and entered into a database validated by the CRO for eCRFs.

The sponsor or its designee will supply the study site with eCRFs. The sponsor or its designee will make arrangements to train appropriate study site personnel in the use of the eCRF.

These eCRFs are used to transmit information collected on the performance of this study to the sponsor and regulatory authorities. The eCRFs must be completed in English.

Data will be entered directly into the eCRF by the investigator or study site personnel via a single data entry process. Study site personnel will be granted access to the eCRF system through a personal user identification and password assigned by the system administrator. In the eCRF, subjects will be identified by their subject numbers. The eCRF is to be dated and signed electronically by the investigator or a qualified person who has been delegated by the investigator to do so on his/her behalf, as documented on a signature delegation log filed in the investigator site file. Data entered in the eCRF will be stored in a centralized database on a remote server.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by designees of the sponsor and will be answered by the site.

Corrections to the eCRF database are recorded in an audit trail that captures a complete record of all information. The new information, identification of the person making the correction, the date the correction was made, and the reason for change are captured in a new record.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered into the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the clinical monitor. The sponsor and/or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Further information on handling of the eCRF data (e.g., data entry, clarification, and validation) will be defined in the data management plan

13.2 ARCHIVING

Because the study is being conducted to obtain marketing authorization, the requirements of ICH Guideline E6 section 5.5.11 and 5.5.12 shall be taken into account.

The investigator is responsible for archiving the investigator site file, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 10 years, but should be retained for longer if required by regulatory stipulations or by agreement with the sponsor.

If the investigator can no longer maintain the archive of study records (e.g., due to retirement or relocation), the sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records must not be destroyed without prior written consent from the sponsor.

14 SUPERVISION OF THE CLINICAL STUDY

14.1 ACCESS TO SOURCE DATA

According to ICH guidelines for GCP and the applicable laws, the investigator must permit all authorized third parties access to the study site and the medical records of the study subjects (source data). These include the clinical monitors, auditors, and other authorized employees of the sponsor as well as members of the local or federal authorities. All these persons are bound to strict confidentiality.

14.2 MONITORING

Monitoring of the study sites will be performed by a CRO designated by the sponsor and will be based on the CRO's monitoring standard operating procedures (SOPs) as well as the study-specific Monitoring Manual.

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. The monitor will visit the study site at periodic intervals and, in addition, the monitor will be adequately trained and maintain contact with the study site via telephone calls as well as in written form, as appropriate. The monitor will be adequately trained and maintain a working knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and study site personnel. Source data review and verification of the most important parameters will be performed for all subjects as described in the Monitoring Manual. The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will report via the project manager of the sponsor-designated CRO to the sponsor who carefully monitors all aspects of the study for compliance with applicable government regulations, with respect to current ICH guidelines for GCP and current SOPs.

Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will need to have eCRFs and source documents available on request.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify the appointed CRO/Monitor of any audits that will be scheduled with any regulatory authority.

The clinical monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the clinical monitor to ensure that corrective and preventative action is taken to resolve any problems noted in

the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., correspondence, clinical study materials, supply shipping manifests, or monitoring logs). An investigator site file will be provided with instructions for the maintenance of study records.

14.3 INDEPENDENT DATA MONITORING COMMITTEE

An unblinded IDMC will be established to allow regular monitoring of the study data to detect and report early evidence of unanticipated harm to subjects.

The safety of the subjects will be monitored by an unblinded IDMC. The IDMC will review the safety data of subjects who have completed the IMP administration in Week 16 and after subjects complete the Follow-up Period. The time points for the IDMC reviews will be defined in the IDMC charter. Safety analyses will be provided by an unblinded statistician.

The reviews will focus on the evaluation of the safety data, including but not limited to TEAEs, drug exposure, laboratory test results, and vital signs measurements, based on the analysis performed by an unblinded statistician. Further details of the data and outputs to be provided to the IDMC will be described in the IDMC charter. Further details on the IDMC membership, the responsibilities of the IDMC, the purpose and timing of the reviews, and the procedures for ensuring confidentiality and proper communication will also be provided in the IDMC charter. The charter will also outline the required content of the written report to be provided by the IDMC after each safety review, including their recommendations for the future conduct of the study.

14.4 AUDITS

In order to guarantee that the conduct of the study is in accordance with ICH guidelines for GCP and the national laws, audits may be performed at the study sites to be carried out by an independent auditor. In addition, for-cause audits may be scheduled.

The investigator agrees to give the auditor access to all relevant documents for review.

14.5 INSPECTIONS

According to the corresponding ICH guidelines for GCP, inspections of the study sites may be performed by the local or regulatory authorities at any time during or after

completion of the study. The investigator will contact the sponsor or designated CRO immediately upon knowledge of a planned inspection.

The investigator agrees to give the inspectors access to all relevant documents for review.

15 DATA PROTECTION AND CONFIDENTIALITY

Within this study, personal data from the study subjects and data regarding the treatment and the course of subject's welfare will be collected.

The data will be stored and processed in anonymized form (i.e., without reference to the subject's name) with the aid of a unique subject identification number.

Data will be managed by a sponsor-designated CRO (data entry, data cleaning, and data exports). The safety concept ensures among other things that data access is limited to authorized persons, that measures are taken to prevent loss of data, and that the applicable laws pertaining to data protection are observed. The data are protected from third party access and only members of the study team are permitted access. These members are bound to strict confidentiality.

Personal data will be stored in an anonymous manner after reaching finishing completion status of all concomitant scientific projects for at least 15 years, if no other or new regulatory requirements come into effect warranting different time periods for archiving.

15.1 DECLARATION REGARDING DATA PROTECTION

During data entry, processing, and analysis by a sponsor-designated CRO, all requirements of the data protection act will be taken into account. Access to data is strictly limited to authorized persons. Data are protected against unauthorized access according to current federal legislation and regulations.

15.2 DECLARATION REGARDING THE ANONYMIZED TRANSFER OF PERSONAL DATA

During data entry, processing, and analysis by a sponsor-designated CRO, all requirements of the data protection act will be taken into account. Access to data is strictly limited to authorized persons. Data are protected against unauthorized access according to current federal legislation and regulations.

16 ADMINISTRATIVE AGREEMENTS

16.1 ADHERENCE TO THE PROTOCOL/PROTOCOL DEVIATIONS

The clinical study described here will be conducted and analyzed in accordance with local laws and ICH guidelines for GCP.

After a subject has been enrolled, it is the investigator's responsibility to avoid protocol deviations in order to obtain unbiased data for the analysis of the study.

All protocol deviations will be documented and discussed with the responsible biostatistician before closing the database and carrying out the statistical analyses.

16.2 FINANCING AND INSURANCE

The study is financed by the sponsor.

The subjects are covered by an applicable insurance policy for participation in a clinical study. One copy of the insurance policy and the insurance conditions will be handed out to the subject and one will be filed in the investigator site file.

16.3 NOTIFICATION OF THE LOCAL AUTHORITIES

The sponsor, their contractors, and all investigators and their deputies are responsible for notifying the local regulatory authority of their participation in the study prior to enrollment of the first subject in the study. Responsibility for notification to the local authorities has been delegated to a sponsor-designated CRO.

This extends also to amendments, discontinuation of study arms or of the entire study, and the regular conclusion of the study.

16.4 PUBLICATION POLICY AND REGISTRATION

16.4.1 Publication Policy

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Study Agreement for the study.

The first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol.

The sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not inadvertently

divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include investigators from study sites that contributed data as well as relevant personnel from the sponsor. Ownership of all data will remain with the sponsor.

Furthermore, the publication policy will follow the recommendations of Good Scientific Practice of the Deutsche Forschungsgemeinschaft (www.dfg.de) and will meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org).

16.4.2 Registration

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for randomization into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

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18 APPENDICES

18.1 CHAPEL HILL CONSENSUS CONFERENCE

DIAGNOSTIC CRITERIA

Widely accepted diagnostic criteria, as opposed to classification criteria or definitions, have not yet been developed for Wegener's granulomatosis (GPA) and microscopic polyangiitis (MPA). In 1994, the CHCC developed definitions for these vasculitides and some of their mimickers [Jennette 1997]. These definitions, along with the American College of Rheumatology Criteria for the classification of vasculitides, are useful in formulating the diagnostic criteria that will be applied to determine a participant's eligibility for this clinical study [Fries 1990].

Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis

- Necrotizing vasculitis with few or no immune deposits affects small vessels (i.e., capillaries, venules, or arterioles).
- Necrotizing arteritis involving small and medium-sized arteries may be present.
- Necrotizing glomerulonephritis is very common.
- Pulmonary capillaritis often occurs.

ACR Criteria for the Classification of Wegener's Granulomatosis

Among a group of patients with various forms of systemic vasculitis, the presence of at least two of these four criteria is associated with a sensitivity of 88.2% and a specificity of 92.0% for WG.

- Nasal or oral inflammation: painful or painless oral ulcers or purulent or bloody nasal discharge
- Abnormal chest radiograph: nodules, fixed infiltrates, or cavities
- Urinary sediment: microhematuria or red cell casts
- Granulomatous inflammation on biopsy: granulomatous inflammation within the wall of an artery or in the perivascular area

ACR Criteria for the Classification of Churg-Strauss Syndrome

Although we wish to exclude Churg-Strauss syndrome (CSS) from this study, we will use the following ACR criteria for the classification of this disorder:

Among a group of patients with various forms of systemic vasculitis, the presence of at least four of these six criteria is associated with a sensitivity of 85.0% and a specificity of 99.7% for CSS.

- Asthma: wheezing or high-pitched rales

- Eosinophilia: >10% of white blood cell differential
- Mononeuropathy or polyneuropathy: mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to vasculitis
- Pulmonary infiltrates, nonfixed: migratory or transitory pulmonary infiltrates
- Paranasal sinus abnormality: acute or chronic paranasal sinus pain, tenderness, or radiographic opacification
- Extravascular eosinophils: biopsy, including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas

18.2 MAJOR SIDE EFFECTS ASSOCIATED WITH GLUCOCORTICOID THERAPY

Body System/ Adverse Event	
Dermatologic and soft tissue	
Skin thinning and purpura Cushingoid appearance Alopecia Acne	Hirsutism Striae Hypertrichosis
Eye	
Posterior subcapsular cataract Elevated intraocular pressure/glaucoma	Exophthalmos
Cardiovascular	
Arrhythmias (with intravenous pulse therapy) Hypertension	Perturbations of serum lipoproteins Premature atherosclerotic disease
Gastrointestinal	
Gastritis Peptic ulcer disease Pancreatitis	Steatohepatitis Visceral perforation
Renal	
Hypokalemia Fluid volume shifts Genitourinary and reproductive Amenorrhea/infertility	Intrauterine growth retardation Bone Osteoporosis Avascular necrosis
Muscle	
Myopathy	
Neuropsychiatric	
Euphoria Dysphoria/depression Insomnia/akathisia	Mania/psychosis Pseudotumor cerebri
Endocrine	
Diabetes mellitus	Hypothalamic-pituitary-adrenal insufficiency
Infectious disease	
Increased risk for typical infections Opportunistic infections	Herpes zoster

18.3 BIRMINGHAM VASCULITIS ACTIVITY SCORE VERSION 3.0

Case Number:

Name: **Date of assessment:**

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.

If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner

Is this the patient's first assessment? **Yes** ☐ **No** ☐

	None	Active disease
1. General	☐	
Myalgia		☐
Arthralgia / arthritis		☐
Fever ≥38° C		☐
Weight loss ≥2 kg		☐
2. Cutaneous	☐	
Infarct		☐
Purpura		☐
Ulcer		☐
♦Gangrene		☐
Other skin vasculitis		☐
3. Mucous membranes / eyes	☐	
Mouth ulcers		☐
Genital ulcers		☐
Adnexal inflammation		☐
Significant proptosis		☐
Scleritis / Episcleritis		☐
Conjunctivitis / Blepharitis / Keratitis		☐
Blurred vision		☐
Sudden visual loss		☐
Uveitis		☐
♦Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)		☐
4. ENT	☐	
Bloody nasal discharge / crusts / ulcers / granulomata		☐
Paranasal sinus involvement		☐
Subglottic stenosis		☐
Conductive hearing loss		☐
♦Sensorineural hearing loss		☐
5. Chest	☐	
Wheeze		☐
Nodules or cavities		☐
Pleural effusion / pleurisy		☐
Infiltrate		☐
Endobronchial involvement		☐
♦Massive haemoptysis / alveolar haemorrhage		☐
♦Respiratory failure		☐

	None	Active disease
6. Cardiovascular	☐	
Loss of pulses		☐
Valvular heart disease		☐
Pericarditis		☐
♦Ischaemic cardiac pain		☐
♦Cardiomyopathy		☐
♦Congestive cardiac failure		☐
7. Abdominal	☐	
Peritonitis		☐
Bloody diarrhoea		☐
♦Ischaemic abdominal pain		☐
8. Renal	☐	
Hypertension		☐
Proteinuria >1+		☐
♦Haematuria ≥10 RBCs/hpf		☐
Creatinine 125-249µ/L(1.41-2.82mg/dl)*		☐
Creatinine 250-499 µ/L(2.83-5.64mg/dl)*		☐
♦Creatinine ≥500 µ/L (≥5.66mg/dl)*		☐
♦Rise in serum creatinine >30% or fall in creatinine clearance >25%		☐
***Can only be scored on the first assessment**		
9. Nervous system	☐	
Headache		☐
Meningitis		☐
Organic confusion		☐
Seizures (not hypertensive)		☐
♦Cerebrovascular accident		☐
♦Spinal cord lesion		☐
♦Cranial nerve palsy		☐
Sensory peripheral neuropathy		☐
♦Mononeuritis multiplex		☐
10. Other	☐	
a.		☐
b.		☐
c.		☐
d.		☐
PERSISTENT DISEASE ONLY: (Tick here if **all** the abnormalities are due to persistent disease)		☐

♦ Major items highlighted

References: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM **87**(11):671-8; Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Baillieres Clin Rheumatol **11**(2): 423-46; Mukhtyar C. et al (2009). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3) ARD 2009 68:1827

18.4 GLOSSARY AND SCORING FOR BVAS VERSION 3.0

Glossary and scoring for BVAS (V. 3). GENERAL RULE: disease features are scored only when they are due to active vasculitis, after excluding other causes (e.g. infection, hypertension, etc.). If the feature is due to active disease, it is scored in the boxes. It is essential to apply these principles to each item below. Scores have been weighted according to the severity which each symptom or sign is thought to represent. Tick "Persistent Disease" box if all the abnormalities are due to active (but not new or worse) vasculitis. If any of the abnormalities are due to new/worse disease, DO NOT tick the "Persistent Disease" box. For some features, further information (from specialist opinion or further tests) is required if abnormality is newly present or worse. Remember that in most instances, you will be able to complete the whole record when you see the patient. However, you may need further information before entering some items. Please leave these items blank, until the information is available, and then fill them in. For example, if the patient has new onset of stridor, you would usually ask an otolaryngologist to investigate this further to determine whether or not it is due to active granulomatosis with polyangiitis (Wegener's).

System/item	Description	New/Worse score	Persistent score
1. General		**3**	**2**
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥ 38.0 ^{0}C	Documented oral/axillary temperature elevation. Rectal temps are 0.5 ^{0}C higher	2	2
Weight Loss	At least 2kg loss of body weight (not fluid) having occurred since last assessment or in the 4 weeks not as a consequence of dieting	2	2

2. Cutaneous		**6**	**3**
Infarct	Area of tissue necrosis or splinter haemorrhages	2	1
Purpura	Petechiae (small red spots), palpable purpura, or ecchymoses (large plaques) in skin or oozing (in the absence of trauma) in the mucous membranes.	2	1
Ulcer	Open sore in a skin surface.	4	1
Gangrene	Extensive tissue necrosis (e.g. digit)	6	2
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	2	1

3. Mucous membranes/eyes		**6**	**3**
Mouth ulcers/granulomata	Aphthous stomatitis, deep ulcers and/or “strawberry” gingival hyperplasia, excluding lupus erythematosus, and infection	2	1
Genital ulcers	Ulcers localized in the genitalia or perineum, excluding infections.	1	1
Adnexal inflammation	Salivary (diffuse, tender swelling unrelated to meals) or lacrimal gland inflammation. Exclude other causes (infection). Specialist opinion may be required.	4	2
Significant proptosis	Protrusion of the eyeball due to significant amounts of inflammatory in the orbit; if unilateral, there should be a difference of 2 mm between one eye and the other. This may be associated with diplopia due to infiltration of extra-ocular muscles. Developing myopia (measured on best visual acuity, see later) can also be a manifestation of proptosis	4	2

Red eye (Epi)scleritis	Inflammation of the sclerae (specialist opinion usually required). Can be heralded by photophobia.	2	1
Red eye conjunctivitis	Inflammation of the conjunctivae (exclude infectious causes and excluding uveitis as cause of red eye, also exclude conjunctivitis sicca which should not be scored as this is not a feature of active vasculitis); (specialist opinion not usually required).	1	1
Blepharitis	Inflammation of eyelids. Exclude other causes (trauma, infection). Usually no specialist opinion is required		
Keratitis	Inflammation of central or peripheral cornea as evaluated by specialist		
Blurred vision	Altered measurement of best visual acuity from previous or baseline, requiring specialist opinion for further evaluation.	3	2
Sudden visual loss	Sudden loss of vision requiring ophthalmological assessment.	6	*
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid) confirmed by ophthalmologist.	6	2
Retinal vasculitis	Retinal vessel sheathing on examination by specialist or confirmed by retinal fluorescein angiography		
Retinal vessel thrombosis	Arterial or venous retinal blood vessel occlusion		
Retinal exudates	Any area of soft retinal exudates (exclude hard exudates) seen on ophthalmoscopic examination.	6	2
Retinal haemorrhages	Any area of retinal haemorrhage seen on ophthalmoscopic examination.		

4. ENT		**6**	**3**
Bloody nasal discharge/ nasal crusts/ulcers and/or granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers and/or granulomatous lesions observed by rhinoscopy	4	2
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses with pathologic imaging (CT, MR, x-ray).	2	1
Subglottic stenosis	Stridor and hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	6	3
Conductive hearing loss	Hearing loss due to middle ear involvement confirmed by otoscopy and/or tuning fork examination and/or audiometry	3	1
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage confirmed by audiometry	6	2

5. Chest		**6**	**3**
Wheeze	Wheeze on clinical examination	2	1
Nodules or cavities	New lesions, detected by imaging.	3	*
Pleural effusion/pleurisy	Pleural pain and/or friction rub on clinical assessment or new onset of radiologically confirmed pleural effusion. Other causes (e.g. infection, malignancy) should be excluded	4	2
Infiltrate	Detected by CXR or CT scan. Other causes (infection) should be excluded	4	2

Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. Other causes such as infection or malignancy should be excluded. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	4	2
Massive haemoptysis/ alveolar haemorrhage	Major pulmonary bleeding, with extensive pulmonary infiltrates; other causes of bleeding should be excluded if possible. Patients are usually in extremis. Do not record minor episodes of haemoptysis.	6	4
Respiratory failure	Dyspnoea which is sufficiently severe as to require artificial ventilation	6	4

6. Cardiovascular		**6**	**3**
Loss of pulses	Loss of pulses in any vessel detected clinically; this may include loss of pulses leading to threatened loss of limb	4	1
Valvular heart disease	Significant valve abnormalities in the aortic mitral or pulmonary valves detected clinically or echocardiographically.	4	2
Pericarditis	Pericardial pain &/or friction rub on clinical assessment.	3	1
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina. Consider the possibility of more common causes (e.g. atherosclerosis)	4	2
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	6	3
Congestive cardiac failure	Heart failure by history or clinical examination	6	3

7. Abdominal		**9**	**4**
Peritonism	Acute abdominal pain with peritonism/peritonitis due to perforation/infarction of small bowel, appendix or gallbladder etc., or acute pancreatitis confirmed by radiology/surgery/elevated amylase	9	3
Bloody diarrhoea	Of recent onset; inflammatory bowel disease and infectious causes excluded.	9	3
Ischaemic abdominal pain	Severe abdominal pain with typical features of ischaemia confirmed by imaging or at surgery, with typical appearances of aneurysms or abnormal vasculature characteristic of vasculitis.	6	2

8. Renal		**12**	**6**
Hypertension	Systolic BP>140 or Diastolic BP>95, accelerated or not, with or without retinal changes.	4	1
Proteinuria	>1+ on urinalysis; >0.2g/24 hours Infection should be excluded.	4	2
Haematuria	10 or more RBC per hpf (high power field), excluding urinary infection and urinary lithiasis (stone)or drug side effects (e.g. cyclophosphamide)	6	3
Creatinine 125-249	Serum creatinine values 125-249 µmol/l (1.41-2.82 mg/dL); only used at first assessment.	4	*
Creatinine 250-499	Serum creatinine values 250-499 µmol/l (2.83-5.64 mg/dL); only used at first assessment.	6	*

Creatinine ≥ 500	Serum creatinine values 500 µmol/l(≥5.66mg/dL) or greater; only used at first assessment.	8	*
Rise in creatinine> 30% or creatinine clearance fall > 25%	Significant deterioration in renal function attributable to active vasculitis.	6	*

9. Nervous system		**9**	**6**
Headache	New, unaccustomed & persistent headache	1	1
Meningitis	Severe headache with neck stiffness ascribed to inflammatory meningitis after excluding infection/bleeding	3	1
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	3	1
Seizures (not hypertensive)	Paroxysmal electrical discharges in the brain & producing characteristic physical changes including tonic & clonic movements & certain behavioural changes.	9	3
Stroke	Cerebrovascular accident resulting in focal neurological signs such as paresis, weakness, etc. A stroke due to other causes (e.g. atherosclerosis) should be considered & appropriate neurological advice is recommended	9	3
Cord lesion	Transverse myelitis with lower extremity weakness or sensory loss (usually with a detectable sensory level) with loss of sphincter control (rectal & urinary bladder).	9	3
Cranial nerve palsy	Facial nerve palsy, recurrent nerve palsy, oculomotor nerve palsy etc. excluding sensorineural hearing loss and ophthalmic symptoms due to inflammation	6	3
Sensory peripheral neuropathy	Sensory neuropathy resulting in glove &/or stocking distribution of sensory loss. Other causes should be excluded (e.g. idiopathic, metabolic, vitamin deficiencies, infectious, toxic, hereditary).	6	3
Motor mononeuritis multiplex	Simultaneous neuritis of peripheral nerves, only scored if motor involvement. Other causes should be excluded (diabetes, sarcoidosis, carcinoma, amyloidosis).	9	3

10. Other	Other features of active vasculitis-please describe. Remember that you should review the rest of the BVAS item list before writing the feature in this section because it may already have been described elsewhere on the form. Do not use this section to record laboratory, imaging or pathology findings. Items recorded in this section will not carry any value when calculating the BVAS score	**0**	**0**

**For some BVAS items, we do not provide recording or scoring of persistent items, either because the item is by definition new/worse, or for renal disease, can only reliably be recorded as new/worse on the first visit*

18.5 OTHER MULTISYSTEM AUTOIMMUNE DISEASES

Prohibited Diseases	Permitted Diseases
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) according to the definitions of the CHCC	Rheumatoid arthritis without systemic and non-articular manifestations (1)
Systemic lupus erythematosus	Ankylosing spondylitis without systemic and non-articular manifestations (2)
IgA vasculitis (Henoch-Schönlein)	Autoimmune thyroiditis (Hashimoto)
Rheumatoid vasculitis	Diabetes mellitus type 1
Sjögren's syndrome	
Cryoglobulinemic vasculitis	
Autoimmune hemolytic anemia	
Mixed connective tissue disease	
Autoimmune lymphoproliferative syndrome	

If any other multisystem autoimmune disease is not listed, please contact the responsible medical monitor for further decisions.

(1) Including, but not limited to: gastrointestinal, pulmonary, cardiac, renal, neurological, skin and ocular manifestations due to RA.

(2) Spine and joints may be affected.

18.6 VASCULITIS DAMAGE INDEX

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***usually have a VDI score of zero,*** unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse since the onset of vasculitis

1. Musculoskeletal	**No**	**Yes**
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertention		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericaritis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name
Trial Number
Date
Centre

7. Peripheral vascular disease	**No**	**Yes**
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

VDI Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI … Arthritis Rheum 40: 371-380

18.7 PHYSICIAN GLOBAL ASSESSMENT

The Physician Global Assessment scale is an 11-point scale to record the assessment of the overall disease activity of the subject. The investigator should not be influenced by the presence of any accumulated damage, complication of treatment, social/emotional problems, or other issues not related to GPA or MPA.

Mark to indicate the amount of GPA or MPA disease activity (not including longstanding damage) within the previous 28 days:

	0	1	2	3	4	5	6	7	8	9	10	
Remission	○	○	○	○	○	○	○	○	○	○	○	**Maximum activity**

18.8 36-ITEM SHORT FORM SURVEY

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

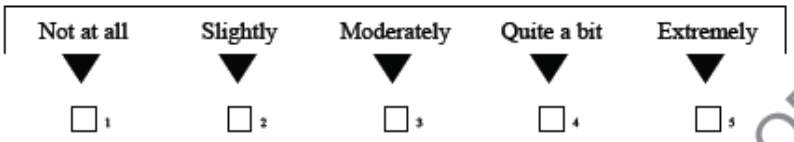
4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

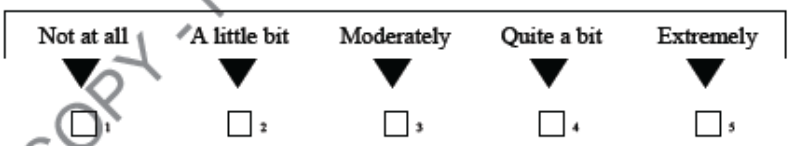
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

18.9 GLUCOCORTICOID TOXICITY INDEX

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	–8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	–8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	–10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	–9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	

Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		Perforation
		Peptic ulcer disease
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	35-400	

BMI, body mass index; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index.